Medical Lib. DEC 16 1926

VOLUME 38 NUMBER 6

ARCHIVES

OF

INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston — WARFIELD T. LONGCOPE, Baltimore

GEORGE DOCK, Pasadena, Calif. — WALTER W. PALMER, New York City

W. S. THAYER, Baltimore

DECEMBER 15, 1926

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $5.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

NOTICE

1927 SUBSCRIPTIONS NOW DUE

Inserted in this issue of ARCHIVES OF INTERNAL MEDICINE *is a pink slip. It is a notification that subscriptions for the coming year are now due and payable. Those who have already paid for 1927 naturally will disregard the notice.*

The names and subscription prices of all of the other journals published by the American Medical Association are printed on the slip. This is for the convenience of those who subscribe for more than one journal. The names of the other journals desired may be written on the blank lines or a check mark may be placed in front of the names as printed in the list. The entire amount of the subscriptions for the various publications thus may be covered by one check or draft and sent with the pink slip.

COPYRIGHT, 1926, BY THE AMERICAN MEDICAL ASSOCIATION

Archives of Internal Medicine

VOLUME 38 DECEMBER, 1926 NUMBER 6

ANALYSIS OF HEART SOUNDS*

H. B. WILLIAMS, M.D.

AND

H. F. DODGE, S.B., A.M.

NEW YORK

Certain sounds pertaining to the heart and lungs are heard in all normal persons. These normal sounds vary in quality and intensity for different individuals depending on the physical make-up of the particular organs producing them and also on the structure of bone and flesh through which the sounds are transmitted to the surface of the body. Pathologic changes can often be detected by the modification of the normal sounds or by the appearance of abnormal sounds. In this article, consideration is given to the nature of normal and abnormal heart sounds with a view to presenting preliminary information relative to their quality and frequency characteristics.

Sound is a form of vibrational energy. Sounds are created by vibrating bodies of some sort and travel through gases, liquids or solid matter in the form of compressional waves. As these waves progress through a medium they become weakened, partly because their energy is spread over a larger area as the distance from the source of sound is increased and partly by loss of energy in the particles which are set into vibration. The distance to which they will travel before the energy becomes imperceptibly small is obviously dependent on the nature of the medium through which they are being transmitted. When the path of the sound waves is abruptly changed in character, as from a liquid to a gas, much of the energy is reflected and only a small portion is passed along into the new medium. Another factor to be considered in connection with the subject at hand is that of distortion of the sounds. Distortion can be produced in certain mediums when discrimination is shown to vibrations of different frequencies, for example, if the material in the path of the waves responds more readily to low frequency than to high frequency vibrations.

In the human body the paths along which the heart and chest sounds can travel to reach the surface of the flesh are many. Much of the

* From Columbia University College of Physicians and Surgeons and the Bell Telephone Laboratories, Incorporated.

energy never gets to the surface, but considering the energy that is available at the surface for auscultation, there is always a "path of least resistance" from the source of sound. The end of this path is picked out by the physician when the point of maximum intensity is found with his stethoscope. By experience it has been found that murmurs produced by lesions in the several valves of the heart are heard best in definite areas on the surface, although these areas are by no means always the nearest to the valves in question. There appear to be "characteristic areas of propagation" on the body surface which can be mapped out for particular types of lesions.[1] Furthermore, the quality of the same sounds as heard in these various areas may be materially different, dependent doubtless on the nature of the particular routes traversed by them.

1. THE NORMAL HEART SOUNDS

With the electric stethoscope described in a recent article,[2] it is possible to reproduce the heart sounds electrically This apparatus consists essentially of an electromagnetic detector or transmitter for picking up the sound vibrations, an amplifier for magnifying the minute electrical vibrations produced in the transmitter, and a group of electric filters for narrowing down the frequency bands of observation in order to reduce the amount of extraneous and interfering noises outside the frequency range of interest. The complex electrical waves thus produced are much more easily handled for study and analysis than the original sound waves, in view of greater facility of controlling electrical energy.

Knowledge of the frequency characteristics of heart sounds will be helpful for determining the essential requirements of any apparatus whether electrical or mechanical to be used for transmitting or reproducing them. It is of even greater importance that we know more exactly the nature of the different body sounds in order to gather fundamental data concerning organic lesions or functional disturbances with which the sounds are associated.

The first heart sound is believed to be due to vibrations set up by the heart muscle at the beginning of contraction. The second or diastolic sound is undoubtedly due to the closure of the semilunar valves.

Studies have been made of the frequency distribution of the energy of normal heart sounds as heard at the apex for ten male adults. The apparatus used for this purpose consisted of the electric stethoscope [2] and a special electrical frequency analyzer which made it possible to determine the relative amounts of energy in the different frequency

1. Cabot, R. C.: Physical Diagnosis, chapter X.

2. Frederick, H. A., and Dodge, H. F.: The Stethophone, an Electrical Stethoscope, Bell System Tech. J. **3**:531-549 (Oct.) 1924.

components of the complex electrical waves. This work has been restricted to a study of the energy above 50 cycles (vibrations per second) and chart 1 shows how the energy above this point is distributed in frequency bands of 10 cycles in width. Indications of later work point out that there is a considerable amount of energy below this point. Although data were obtained for frequencies up to 300 cycles, such a small percentage of the energy lies in 10-cycle bands above 150 cycles, that it is not possible to show the values on this chart.

The relative amount of higher frequency energy varied considerably in the ten persons. We found, for example, that in the cases in which the heart sounds were richest in high frequency components there was

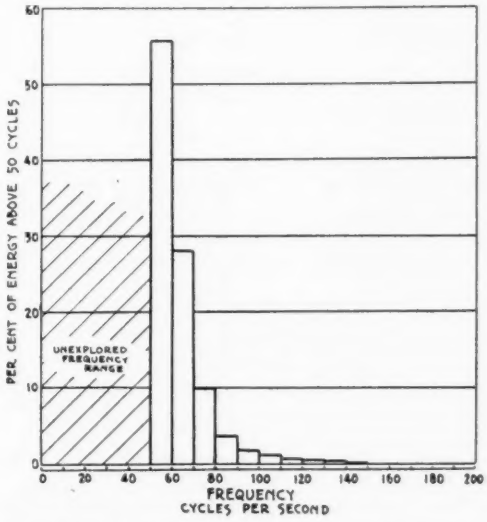


Chart 1.—Energy distribution of normal heart sounds average for ten adult males.

one-tenth the amount of energy in the band 90 to 100 cycles compared with the energy between 50 to 60 cycles and in the band 190 to 200 cycles, about one one thousandth of that energy. In the other extreme case in which the sounds were poorest in high frequency components, the amount of energy in the band 90 to 100 cycles was one one thousandth of the energy in the 50 to 60 cycle band and between 190 to 200 cycles, approximately one one-hundred thousandth of that energy. This variation in the distribution of the vibrational energy is what determines the characteristic qualities of the heart sounds of different persons.

It is important to note that the actual distribution of energy shown in chart 1 will appear as such only when measured or recorded by instruments that are equally sensitive to all frequencies within this range. Such an instrument is the Einthoven galvanometer, which may be used to produce graphic records, examples of which will be presented in a later article. But when we observe these vibrations by ear as during auscultation, a new set of conditions exists. The normal heart sounds as heard in the physician's stethoscope are so faint that they may be considered near the threshold of audibility. For sounds near the threshold of audibility, the ear is much less sensitive to low frequency than to higher frequency sounds.[3] For example, if we consider the relative sensitivity of the ear near the threshold of audibility,

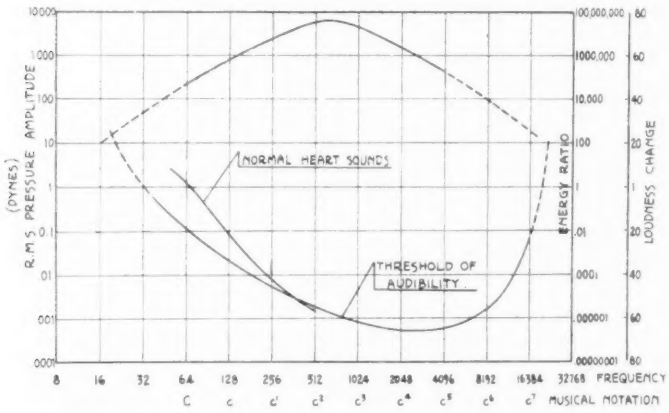


Chart 2.—Normal heart sounds and the characteristics of hearing.

we find that it takes over 100 times as much sound energy [4] at 50 cycles to produce the same auditory sensation as at 150 cycles. This is a particularly important consideration for the frequency range of interest in auscultation.

Thus, if we take into account the characteristics of the ear, we get a new picture of the relative importance of the different frequency components with respect to their shares in contributing to the total loudness. Perhaps the best picture can be obtained by the curve of normal heart sound energy in conjunction with the chart of normal

3. Wegel, R. L.: The Physical Characteristics of Audition, Bell System Tech. J. **1,** November, 1922. Fletcher, H.: Physical Measurements of Audition and Their Bearing on the Theory of Hearing, J. Franklin Inst. **196,** September, 1923.

4. More rigorously "power" rather than "energy." If, however, all the sounds that are compared are of the same duration, comparisons will be numerically the same whether power or energy is measured.

auditory sensation area [5] as given by measurements of hearing (chart 2). The sensation value to the ear at any frequency for the heart sounds is measured by the difference between the average heart sound curve and that of the threshold of audibility. Where the heart sound curve drops below the threshold curve, the components are not audible. Due to the greater sensitivity of the ear at higher frequencies, the small amount of energy between say 100 and 300 cycles is of considerably greater importance than would appear from chart 1. For example, let us compare the two bands, 50 to 60 cycles and 140 to 150 cycles. From chart 1 it is seen that the relative energy of the heart sounds in these two bands is of the order of 400:1. Yet, due to the greater sensitivity of the ear in the latter region, the relative sensation is considerably less than 10:1. From chart 2 we can see at a glance over what frequency range the audible components of average normal heart sounds extend. Since the ear is customarily employed for observing the heart sounds, these factors must be considered carefully in the interpretation of any data obtained by instruments of different characteristics.

The normal heart sounds of different persons have their own peculiar quality characteristics somewhat as various voices do. The quality of these two kinds of sounds is a function of the frequency distribution of the energy of which they are composed. Speech is produced by the vibration of the vocal cords, but the sounds so produced are subsequently modified as they pass through the vocal passages of the throat and mouth. Thus, the mode of vibration of the organs of speech and the configuration of the paths through which the sounds are propelled are factors which make one voice fundamentally different from another. In much the same way, the mode of production of the heart sounds and the nature of the path traversed by them gives the unique characteristics for different persons. For comparative purposes, the distribution of energy in connected speech is shown in chart 3. The data for this chart are taken from a composite curve of connected speech for four male and two female voices.[6] Chart 3 should be compared directly with chart 1 for it represents distribution of energy and does not consider the characteristics of the ear. For speech, most of the energy is concentrated at relatively low frequencies, but the higher frequency elements up to 5,000 cycles are of great importance in determining the quality of the sounds produced. This is substantially the case for the normal heart sounds, but the frequencies in this case are far lower and, for all practical purposes, the upper frequency limit may be considered as not higher than 400 cycles.

---

5. Fletcher: Footnote 3, second reference.

6. Crandall, I. B., and MacKenzie, D.: Analysis of the Energy Distribution in Speech, Physiol. Rev. **19**:221 (March) 1922.

Aside from the consideration of quality, it may be of some interest to note the relative intensity of normal heart sounds as observed with the electric stethoscope for different persons. It was noted that for thin chested persons more energy was available at the sternum than at the apex, while for those of more solid construction the energy usually was greatest at the apex. In several cases there was no marked difference in the energy in these two areas. For purposes of study about twenty male adults were chosen, more or less at random, without any thought of having cases of extremely loud or extremely weak heart sounds. For each, the area of maximum sound intensity was selected

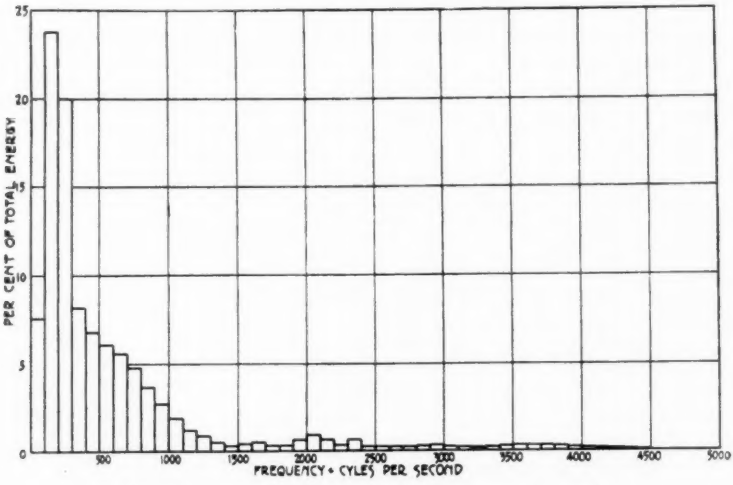


Chart 3.—Distribution of energy in connected speech.

and by suitable electrical measuring apparatus, the sound energy at this point was determined. In this study a ratio of over 40:1 in sound energy was observed between the loudest and the weakest normal heart sounds for the persons in the group.

2. FETAL HEART SOUNDS

So far as we have been able to determine from a limited number of cases at Sloan Hospital in New York City, the frequency composition of fetal heart sounds is similar to that of normal heart sounds. The amount of sound energy is, however, considerably smaller than for normal heart sounds. This can be visualized then by referring to chart 3 and considering the normal heart curve lowered to a position on the chart close to the threshold of audibility curve. For fetal heart sounds, therefore, the ear must operate close to the threshold of audi-

bility, and in extreme cases may be incapable of detecting the sounds. Acuity of hearing at low frequencies is obviously an essential requirement in obstetrical auscultation.

3. HEART MURMURS

The mode of origin and the character of abnormal heart sounds is well known to all physicians.

In a recent article [7] the results of investigating the frequency bands of importance in the abnormal sounds of a large number of hospital cases of heart murmurs were given. The apparatus used in this work consisted of an electric stethoscope [2] provided with a group of special electric filters by means of which it was possible to determine

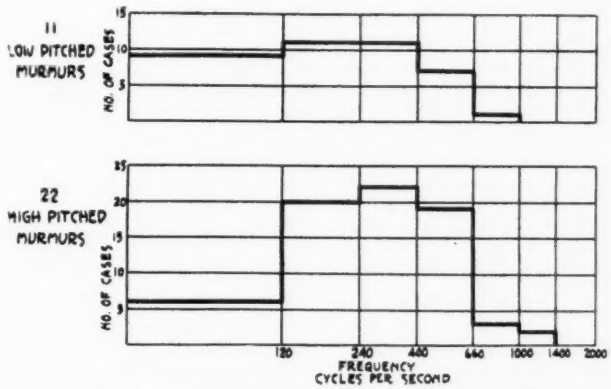


Chart 4.—Composite of frequency bands for murmur sounds.

the frequency band within which all the audible components of the murmur sounds fell.[8] A study of presystolic, systolic and diastolic murmurs showed that, in general, certain fairly broad bands of frequencies could be established within which the murmur sounds of any one of these three groups could be relegated.

It is perhaps desirable to give additional data to indicate the significance of the terms "low pitched" and "high pitched" regardless of whether the sounds are associated with systole or diastole. This has been done in chart 4, data for which were obtained with electric filters

7. Cabot, R. C., and Dodge, H. F.: Frequency Characteristics of Heart and Chest Sounds, J. A. M. A. **84**:1793 (June 13) 1925.

8. By suitable combinations of inductances and capacities, electric circuits can be produced which have the property of transmitting electric vibrations of different frequencies in a selective fashion. These circuit devices have become known as electric filters, since their action is analogous to that of a filter.—Campbell, G. A.: Physical Theory of Electrical Wave Filters, Bell System Tech. J., November, 1922.

by the same general method as outlined in the previous article. In this figure, the composite charts are made up by adding together the frequency bands corresponding to eleven low pitched murmurs and twenty-two high pitched murmurs. The first shows that for eleven low pitched murmurs there were always components of sounds in the band 120-400 cycles per second and in nine out of eleven there were components up to 120 cycles per second. Broadly, we can think of low pitched murmurs as covering a range up to 400 cycles per second. The second chart shows that for twenty-two murmurs described as "moderately high" or "high pitched" there were always components of sound within the band 240-400 cycles per second, and nineteen times out of twenty-two, components within the band 240-660 cycles per second. From this we can consider the band 120-660 cycles as of greatest general importance for high pitched murmurs.

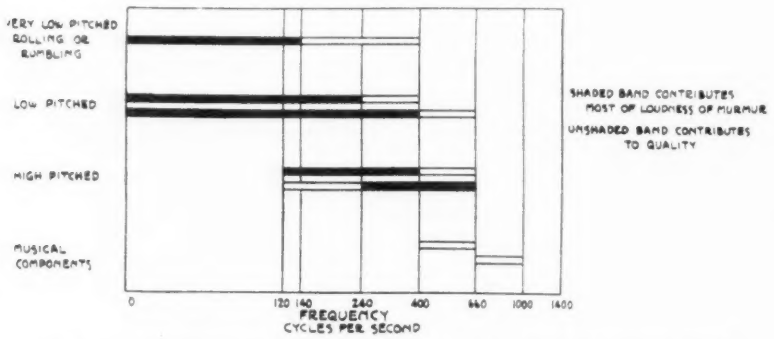


Chart 5.—Representative frequency bands of certain classes of murmur sounds; shaded band: contributes most of loudness of murmur; unshaded band: contributes to quality.

The energy of the murmur sounds is by no means distributed uniformly over the frequency band within which all the audible components are situated.[7] If it were possible to plot a frequency distribution curve of the energy, we should undoubtedly find the shapes of the curves materially different for all murmurs. For any particular case, in a certain relatively narrow band we should find a rather large percentage of the total energy of the complex sounds and outside of this band a tapering off of energy to frequency points beyond which the amount was insufficient to give any audible sensation to the ear. It is important to note that, although the components of the sounds within such a narrow band are of major importance in fixing the "pitch" and in producing the total loudness, the remaining components outside this band are important factors in determining the quality of the sounds as a whole.

By means of electric filters and the same general method described in a previous article,[7] we have been able to obtain a rough idea of how the total energy of murmur sounds is distributed over the frequency band which is associated with a given murmur. The method consisted in introducing into the circuit of the electric stethoscope low pass filters with successively lower cut-off frequencies and then high pass filters with successively higher cut-off frequencies and observing the resulting change in loudness without any regard for the corresponding change in quality. It was found that murmurs described as "low pitched" (or "high pitched") as a class differ greatly among themselves, depending on whether they are characterized as blowing, rasping or whistling. The results are indicated in chart 5 in which are shown the frequency bands most frequently associated with murmurs described as (1) "very low pitched, rolling or rumbling," (2) "low or moderately low pitched," (3) "high or moderately high pitched" and (4) "with musical components." The shaded portion indicates the frequency band which contributes most of the loudness while the unshaded portion indicates the band which is important only from the standpoint of quality of the complex sounds as a whole. For many individual cases the shaded portion could be narrowed down still further. Whenever the pitch could be identified with a particular musical note, it was found to correspond to some frequency within the shaded portion.

This chart indicates that most of the energy of murmur sounds is made up of frequencies below 660 cycles per second. Occasionally, components of sound are present above this frequency, particularly musical components, but these do not usually have any particular relation to the more energetic constituents of the murmur.

THE MECHANISM OF PAIN IN GASTRIC AND IN DUODENAL ULCER

II. THE PRODUCTION OF PAIN BY MEANS OF CHEMICAL IRRITANTS

WALTER LINCOLN PALMER, M.D.
CHICAGO

Experimental data are presented here regarding the rôle of chemical irritants in the production of ulcer distress. Gastric ulcer and duodenal are considered together because the mechanism of pain in each has been found to be essentially the same.

LITERATURE

The older clinicians, like Talma [1] and Riegel,[2] apparently felt that the pain of uncomplicated ulcer was in some way related to the acidity of the gastric content, but they recognized gastric peristalsis and coarse food as possible additional factors. These men debated, not the mechanism of ulcer pain, but rather the occurrence of pain from hyperacidity without a definite organic lesion. Lowenthal,[3] Schmidt,[4] Boring [5] and Hurst [6] introduced various amounts of hydrochloric acid into the stomach in strengths varying from 0.5 to 2 per cent. They failed to produce pain either in normal persons or in patients with ulcer. Hardt [7] reported that distress caused by ulcer might even be relieved by 0.3 per cent hydrochloric acid. Reynolds and McClure [8] poured acid directly onto a duodenal ulcer by means of a Rehfuss tube without producing pain. These negative results were widely accepted as conclusive evidence against the acid origin of gastric distress. Bonminger [9] had reported in 1909, however, that the distress of gastric ulcer could be brought on regularly by the introduction into the empty stomach of from

1. Talma: Zur Behandlung von Magenkrankheiten, Ztschr. f. klin. Med. **8**:407-417, 1884.
2. Riegel: Nothnagel's System of Medicine, Diseases of Stomach, London, W. B. Saunders Company, 1915, p. 579.
3. Lowenthal: Berl. klin. Wchnschr. **29**:1188, 1892.
4. Schmidt, J. E.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **19**:278, 1909.
5. Boring: Am. J. Psychol. **26**:48 (Jan.) 1915.
6. Hurst, A. F.: The Sensibility of the Digestive Tract, London.
7. Hardt, L. L. J.: Pain in Active Pathologic Processes in Stomach or Duodenum, J. A. M. A. **70**:837 (March 23) 1918.
8. Reynolds, L., and McClure, C. W.: Motor Phenomena Occurring in Normal Stomachs, in Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically, Arch. Int. Med. **29**:1-11 (Jan.) 1922.
9. Bonminger: Berl. klin. Wchnschr. **45**:396, 1909.

100 to 200 cc. of decinormal hydrochloric acid. This work was overlooked, apparently, or at least it was overshadowed by the numerous negative results. Sippy [10] found clinically that the pain of ulcer was practically always associated with a rather high degree of free acid in the gastric content obtained at the time of distress. He admitted that an equally high free acidity might be present at other times without distress. This he explained on the basis of decreased sensitiveness of the exposed nerve endings.

THE EFFECT OF ACID INJECTIONS IN NORMAL STOMACHS

The fact that gastric distress is not experienced every day by persons with perfectly normal stomachs, the contents of which may have a relatively high degree of free acid, is in itself conclusive evidence that normal gastric acidities do not produce distress in the normal stomachs of normal persons. Observations with stronger solutions have been made by other observers, as has been noted, but more information is necessary if one contemplates a comparative study of the effect of acid solutions in different types of stomachs. Normally, the gastric free acidity rarely exceeds 0.5 per cent. Hence, a study was made of the effect of injecting acid of this strength into thirty normal empty stomachs by means of a Rehfuss tube. The unit of concentration was 0.5 per cent hydrochloric acid; the unit of amount was 200 cc.; the unit of time, thirty minutes; the usual number of injections in each experiment, two; the total amount of acid given, 400 cc.; the total length of the experiment, one hour. The results are shown in table 1. In twenty-nine of these patients, there was no sensation comparable to ulcer distress; in one, a slight burning developed; in seven, nausea was present; and in four, vomiting occurred. In a later series, it was thought that the percentage experiencing a slight burning was rather higher than in this first series. In one case in which acid was injected into the lower end of the esophagus, an intense burning was noticed. Nausea and vomiting seemed to occur only when the acid entered the duodenum. The injection of acid directly into the duodenum resulted in nausea, retching or vomiting almost immediately in a high percentage of cases. Large amounts of 0.5 per cent acid, 600 cc. or more, were frequently retained in the normal stomach for an hour or longer without distress other than a sensation of a slight burning or warmth in the epigastrium. The pylorus frequently failed to prevent the acid solution from reaching the duodenum in such quantities and concentrations as to cause vomiting. Strong alkalis, such as tenth normal sodium hydroxide, had a similar effect either when introduced into the duodenum directly or when the

10. Sippy, B. W.: Oxford Medicine, New York, Oxford Univ. Press, vol. 3, p. 132.

pylorus failed to retain them in the stomach until neutralization occurred. The pylorus seems to open more readily to alkalis than to acids.

THE EFFECT OF ACID INJECTIONS IN PATIENTS WITH ULCER

In considering the results of similar injections made into the stomachs of patients with ulcer, it is necessary to bear in mind that there are times, apparently, in which the pain producing mechanism of the ulcer is insensitive to the normal stimulus. It may remain so for days, weeks or months. During such periods it might be insensitive to an artificial stimulus as well. This differentiation has been found to be of great importance, as is shown in table 2, which comprises a list of twenty-five patients in whom the acid injections produced no distress other than that seen in normal persons. The old ulcer distress was not reproduced at any time. Thirty-five of the thirty-nine tests were made at a time when the pain producing mechanism was not sensitive to the normal irritant, as was evidenced by the fact that the patient was in a distress-free period. A distress-free period was considered as one in which spontaneous pain was absent for the twenty-four hours preceding the test. Four of the tests were made during a distress period and yet no pain resulted. The length of the experiment was prolonged frequently in the study of this group, 200 cc. of the acid solution being given every thirty minutes for three injections. The stomach was emptied in each case before the first injection and again at the end of the test.

The third table shows the results obtained in eighty-four patients in whom injection of the acid initiated typical ulcer distress 324 times. There were only ten failures in this group in distress periods, as opposed to seventy in distress-free periods. The majority of the distress-free periods were induced by treatment. In those cases in which distress appeared after the first or second injection, the experiment was discontinued without further injections. At times, pain was produced by the injection of small amounts of acid directly into the duodenum at the site of an active sensitive ulcer. The distress produced was in nearly every instance the patient's usual ulcer distress, typical in type and in location, and recognized by him as such. It varied in intensity in the same person and in different persons. In some it was only a mild distress, occasionally barely noticeable. These were usually persons with little spontaneous pain. In others, the distress produced appeared objectively to be as excruciating as that seen in any condition, sufficient to cause the patient to groan, perspire, writhe and even to roll on the floor in extreme agony. This distress would be relieved immediately or within thirty or forty minutes by emptying the stomach or by neutralizing the acid with alkali or cold egg-nog, or by a combination of these procedures.

The evidence that this distress is real ulcer distress is as follows:

1. The patient recognizes it as his typical distress, identical in type and in location with that which he usually experiences.

2. Such distress is not produced by similar injections into normal stomachs.

3. The sensitiveness of the pain producing mechanism decreases as the ulcer heals. This is followed most easily in gastric ulcers with penetrating defects.

4. Ulcers found healed at laparotomy have been found to be acid insensitive before operation in every case tested so far. (The reverse is not true. Open ulcers may be insensitive to the acid as well as to the normal irritant.)

TABLE 1.—*Effect of Injection of Five-Tenths Per Cent Hydrochloric Acid Solution in Control Group*

Number studied	30
Pain produced	0
Slight burning	1
Nausea	7
Vomiting	4

TABLE 2.—*Patients with Ulcer in Whom Typical Distress Was Not Produced by the Injection of Five-Tenths Per Cent Hydrochloric Acid Solution*

Location of Lesion	Number of Patients	Failures	
		In Distress Period	In Distress-Free Period
Duodenal	16	4	17
Gastric	8	0	15
Multiple gastric and duodenal	0	..	..
Recurrences after gastro-enterostomy	1	0	3
Total	25	4	35

The seventy failures during a distress-free period are not difficult to understand. Many of them were in persons who had become pain-free on ordinary ward diet, but the majority were in persons who had become pain-free as a result of antacid ulcer therapy. They were acid sensitive prior to the beginning of treatment and gradually became acid insensitive, as was indicated by their ability to tolerate three injections of 200 cc. of 0.5 per cent hydrochloric acid solution, 600 cc. in all, for the entire period of one and a half hours without any of their original ulcer distress. These seventy failures, as well as the thirty-five in table 2, making 105 in all, seemed to be due to a decrease in the sensitiveness of the pain producing mechanism.

The ten failures during a distress period (that is, at a time when spontaneous distress had been present within the preceding twenty-four hours) are perhaps a little more difficult to understand. There were

four such failures in table 2, making a total of fourteen. It is to be noted that eleven of these fourteen occurred in duodenal ulcers. Some of these failures are thought to have been due to persistent closure of the pylorus, as is evidenced by the recovery at the end of the test period of the entire amount of fluid injected. In such cases, the acid did not come into contact with the ulcer, but in others the stomach emptied fairly rapidly, and this explanation does not suffice. It is possible that such failures as well as the three in the gastric ulcer group may have been due to an unusually long latent period. The distress produced by the acid appeared in many instances during the first injection; in others, it appeared several minutes later; and in others it did not appear until after the second or third injection. Perhaps in a few cases in which it did not appear at all, the latent period exceeded the hour or hour and a half which constituted the length of the experiment.

It must be admitted that the concentration of the acid used in these experiments is much higher than that usually encountered in clinical gastric analyses. Can these results be duplicated or confirmed by the use of definitely physiologic concentrations? The following protocol is one of several which show conclusively that it can be.

EXPERIMENT 359.—Patient J. A. Active duodenal ulcer.

11:30 Lunch.
12:45 Pain appeared.
2:00 Pain worse than it had been for weeks.
2:45 Pain somewhat less. Stomach emptied of 50 cc. of gruel. Free acidity, 58; total, 108.
2:52 Pain entirely gone.
3:00 100 cc. of hydrochloric acid solution. Free acidity, 52; total, 55.
3:08 Pain reappeared.
3:22 Pain disappeared.
3:40 Stomach emptied of 50 cc. of gruel. Free acidity, 29; total, 41.
3:50 Pain reappeared.
4:00 Pain very severe.
4:03 Stomach emptied of 75 cc. of liquid. Free acidity, 31; total, 41. Pain relieved immediately.
4:18 100 cc. of hydrochloric acid solution. Free acidity, 40; total, 43.
4:28 Mild distress appeared.
4:35 Pain disappeared. Stomach emptied of 45 cc. of liquid. Free acidity, 33; total, 44.
4:50 100 cc. of hydrochloric acid solution. Free acidity, 30; total, 32.
4:53 Mild distress appeared.
5:20 Pain continued quite severe. Stomach emptied of 25 cc. of clear juice. Free acidity, 35; total, 43.
5:28 Pain entirely gone.
5:30 100 cc. of hydrochloric acid solution. Free acidity, 19; total, 21.
5:45 No distress. Stomach emptied of 70 cc. of liquid. Free acidity, 43; total, 51.
5:54 100 cc. of hydrochloric acid solution. Free acidity, 52; total, 55.
6:05 Pain appeared.
6:07 Pain quite severe, patient groaning. Stomach emptied of 65 cc. of clear liquid. Free acidity, 54; total, 61.
6:21 Pain gone.

Here the typical pain was relieved by emptying the stomach of 50 cc. of gruel with a free acidity of 58; it reappeared after the injection of 100 cc. of acid with a free acidity of 52, and it disappeared when the free acidity of the content fell to 29. Further injections of solutions with free acidities of 51, 40 and 30, all produced distress which was relieved by emptying the stomach. Distress was not produced by a similar amount with a free acidity of 19. It seems probable that it would have resulted within a few minutes if the period of observation had been extended, for the free acidity was rapidly rising, due apparently to active gastric secretion. It did reappear following the injection of a solution whose free acidity was slightly higher, but still lower than that found in the original gastric content. It is apparent, therefore, that ulcer pain which has been relieved by emptying the stomach can be made to reappear by the injection of adequate amounts of hydrochloric acid in strengths no greater than that present at the time of distress, i. e., in perfectly physiologic concentrations.

The previous experiments definitely establish the fact that typical ulcer distress can be initiated by the introduction of a chemical irritant into the stomach at a time when the pain producing mechanism is known to be sensitive to the normal irritant. The chemical irritant used was hydrochloric acid varying in concentration from 0.5 per cent to the perfectly normal and physiologic strengths of 0.2 and 0.1 per cent. Typical ulcer distress was produced and relieved at will by the injection and withdrawal of the acid solutions. If the normal irritant to the pain-producing mechanism resides in the gastric content, withdrawal and reinjection of this material should have an effect similar to that of the acid solutions. The following protocol illustrates one of the several experiments which show that it does have such an effect.

EXPERIMENT 370.—Patient A. G. Active duodenal ulcer.

7:00 Ward breakfast.
9:50 Typical pain appeared.
10:10 Stomach emptied of 140 cc. of thin gruel. Free acidity, 37; total, 77.
10:15 Pain entirely gone.
10:22 120 cc. of gruel emptied at 10:10 reintroduced.
10:40 Pain returned.
10:54 250 cc. of cold egg-nog.
11:00 Pain entirely gone.

Typical distress was present in this experiment, with a normal free acidity of 37; this distress was relieved in five minutes by emptying the stomach; it returned eight minutes after the gruel had been reintroduced, and it was relieved by 250 cc. of cold egg-nog. The gastric content, therefore, does contain a normal irritant to the pain producing mechanism.

If hydrochloric acid is a normal irritant, pain should result at times in sufficiently sensitive mechanisms from the presence in the

stomach of pure gastric juice, especially if the concentration of acid be high. This might occur spontaneously or as a result of the stimulating effect of histamine hydrochloride given hypodermically. Such observations were made and repeatedly confirmed in the manner typified in the following protocol.

EXPERIMENT 393.—Patient C. F. Active duodenal ulcer.

6:33 200 cc. of 0.5 per cent hydrochloric acid. Pain appeared during injection. Stomach emptied immediately of 210 cc. of clear liquid. Free acidity, 150; total, 154. Pain relieved immediately.
6:38 200 cc. of 0.25 per cent hydrochloric acid solution.
6:40 Pain appeared.
6:45 Stomach emptied of 200 cc. of clear liquid. Free acidity, 81; total, 84.
6:47 200 cc. of hydrochloric acid solution. Free acidity, 50; total, 51. Pain appeared during injection; very mild.
6:51 Stomach emptied of 150 cc. of clear liquid. Free acidity, 58; total, 62. The pain was relieved immediately.
6:54 200 cc. of hydrochloric acid solution. Free acidity, 39; total, 40.
7:00 Pain appeared; very mild.
7:03 Stomach emptied of 110 cc. of clear liquid. Free acidity, 48; total, 52.
7:04 Pain gone.
7:07 200 cc. of hydrochloric acid solution. Free acidity, 24; total, 26.
7:18 200 cc. of hydrochloric acid solution. Free acidity, 24; total, 26. Heaviness but no other distress.
7:23 Very faint distress appeared, almost difficult to recognize.
7:26 Stomach emptied of 170 cc. of liquid. Free acidity, 39; total, 42. Distress relieved immediately.
8:15 Pain appeared.
8:23 Stomach emptied of 40 cc. of gastric juice. Free acidity, 82; total, 91.
8:33 Pain entirely gone.
8:50 Stomach emptied of 10 cc. of gastric juice. Free acidity, 89; total, 101.
8:58 1.25 mg. of histamine subcutaneously.
9:07 Pain appeared.
9:10 Stomach emptied of 20 cc. of cloudy gastric juice. Free acidity, 86; total, 93.
9:13 Pain entirely gone.
9:26 Pain appeared, worse than last time.
9:30 Stomach emptied of 55 cc. of cloudy juice. Free acidity, 100; total, 107.
9:40 Pain continued. Stomach emptied of 55 cc. of cloudy juice. Free acidity, 108; total, 116.
9:45 Pain entirely gone.

The patient was seated in a chair during this experiment, and his mind was centered largely on the smoked drum which was revolving before him registering his hunger contractions from time to time. He had no knowledge of the solutions that were being used or of their purpose. His only instructions were to sit still, to avoid coughing if possible, to notify the observer whenever the water manometer failed to work properly, and to indicate the appearance and disappearance of distress. No suggestion was given him as to the time at which he might expect distress or as to what might relieve it. The results obtained were so constant with him and with other patients as well that mental suggestion cannot be considered to have been a factor.

The first half of this experiment again illustrates the production of pain by the injection of physiologic strengths of the acid, and the manner in which the severity of the pain decreases as the acid concentration of the solution decreases until with a free acid of 24 no distress was produced. When the gastric secretion had raised the free acidity to 39, a very faint distress appeared. Here there is a suggestion of a quantitative relationship between the concentration of the acid and the severity of the pain.

In the second part of the experiment, pain appeared spontaneously, and it was relieved by emptying the stomach of 40 cc. of gastric juice having a free acidity of 82. At 9:07, following the histamine injection, pain appeared and was relieved again by emptying the stomach. At 9:26 pain reappeared, more severe than before, but this time it was not relieved by emptying the stomach at 9:30. The reason is obvious, for ten minutes later when the stomach was emptied again another 55 cc. of gastric juice was obtained with a free acidity of 108. Relief was complete five minutes later. Here ulcer distress is clearly shown to have been present when the stomach contained only its own gastric juice, and to have been relieved by the removal of this juice.

Can ulcer distress be initiated by the introduction into the stomach of the gastric juice of another person, and, if so, is there any relationship between its free acidity and its pain-producing power? The following protocol answers the question in an illustrative fashion.

EXPERIMENT 378.—Patient A. G. Active duodenal ulcer.

4:59 200 cc. of 0.5 per cent hydrochloric acid solution.
5:07 Pain appeared.
5:20 Stomach emptied of 240 cc. of clear liquid. Free acidity, 101; total, 109.
5:23 Pain entirely gone.
5:27 100 cc. of gastric juice injected. Free acidity, 95; total, 105. Gastric juice obtained in another patient by histamine stimulation.
5:40 Pain appeared.
5:48 Stomach emptied of 110 cc. of clear juice. Free acidity, 59; total, 70.
5:50 Pain entirely gone.
6:02 200 cc. of gastric juice the acidity of which had been lowered from 100 to 0 by calcined magnesia and sodium bicarbonate.
7:02 No pain. Stomach emptied of 80 cc. of clear light yellow liquid. Free acidity, 32; total, 43.
7:09 200 cc. of 0.25 per cent hydrochoric acid solution.
7:11 Pain appeared.
7:17 Stomach emptied of 225 cc. of clear liquid. Free acidity, 65; total, 72.
7:22 Pain entirely gone.

Here pain was produced by the pure acid solution and relieved by its withdrawal; it was produced again by highly acid gastric juice and relieved by its withdrawal; but it did not result from the injection of gastric juice whose free acidity had been neutralized by alkali.

Since pain resulted alike, therefore, from the introduction into the stomach of acid gastric content, of physiologic concentrations of hydro-

chloric acid, and of highly acid gastric juice, and was relieved by the withdrawal of this solution, and since pain did not result from the same gastric juice when its free acid had been neutralized, it must be concluded that the acid was the irritant common to the three pain-producing solutions, and that it was responsible for the initiation of the pain in each instance.

TABLE 3.—*Patients with Ulcer in Whom Typical Distress Was Produced by Injection of Five-Tenths Per Cent Hydrochloric Acid Solution*

Location of the Lesion	Number of Patients	Successes	Failures	
			In Distress Period	In Distress-Free Period
Duodenal	49	185	7	51
Gastric	29	119	3	12
Multiple gastric and duodenal	2	13	0	3
Recurrence after gastro-enterostomy*	4	7	0	4
Total	84	324	10	70

* Jejunal ulcer proved at operation in one case.

THE EFFECT OF OTHER CHEMICAL IRRITANTS ON THE PAIN-PRODUCING MECHANISM

If the action of the acid is purely that of a chemical irritant it ought to be possible to obtain similar results in sufficiently sensitive mechanisms by means of other chemical irritants. This has been found to be the case. Solutions of sulphuric acid, acetic acid and sodium hydroxide were tried and distress produced, although not with the same constancy as with hydrochloric acid. The solutions of sulphuric acid and of sodium hydroxide gave rather severe distress in some instances, but acetic acid with its very low free acidity and poor ionization gave only mild distress, as is noted in the following protocols.

EXPERIMENT 373.—Patient G. N. Active duodenal ulcer.

4:00 200 cc. of 0.25 per cent hydrochloric acid solution.
4:08 Pain appeared.
4:18 Pain severe; went through to the back. Stomach emptied of 75 cc. of clear liquid. Free acidity, 22; total, 32.
4:25 Pain entirely gone.
5:30 200 cc. of sulphuric acid solution. Free acidity, 99; total, 101.
5:32 Pain appeared.
5:37 Stomach emptied of 160 cc. of clear liquid. Free acidity, 79; total, 86. Pain relieved immediately.
5:43 200 cc. acetic acid solution, approximately 3 per cent. Pain appeared immediately, burning in type, more generalized than the previous distress and associated with nausea.
5:52-6:00 Stomach emptied of 225 cc. clear liquid. Free acidity, 10; total 485.
6:07 Distress entirely gone.

EXPERIMENT 369.—Patient J. A. Active duodenal ulcer.

4:29 55 cc. of gastric juice reinjected. Free acidity, 96; total, 106.
4:33 Pain appeared.

4:39 Pain quite severe. Stomach emptied of 40 cc. of clear liquid. Free acidity, 71; total, 85.
4:53 Pain entirely gone.
4:58 55 cc. of gastric juice emptied. Acidity reduced by sodium hydroxide to free acidity, 6; total, 16.
5:13 Mild distress reappeared.
5:16 Stomach emptied of 50 cc. of clear liquids. Free acidity, 33; total, 48.
5:22 Pain entirely gone.
5:26 100 cc. of tenth normal sodium hydroxide injected. Distress appeared immediately, "pretty bad," and accompanied by nausea.
5:35 Nausea gone; pain continued.
5:39 Pain entirely gone. Stomach emptied of 35 cc. of clear liquid, alkaline to phenolphthalein.

TABLE 4.—*Pain with Other Chemical Irritants*

Location of Lesion	Number of Patients	Successes	Failures
0.4 per cent Sulphuric Acid Solution			
Gastric	2	2	0
Duodenal	2	2	0
Total	4	4	0
3 per cent Acetic Acid Solution			
Gastric	3	3	1
Duodenal	2	2	0
Total	5	5	1
Tenth-Normal Sodium Hydroxide			
Gastric	4	5	5
Duodenal	4	2	2
Gastric and duodenal	2	4	4
Total	10	11	11

TABLE 5.—*Types of Extragastric Abdominal Distress Tested with Acid Injections*

Diagnosis	Number of Cases	Pain Produced by Acid	Pain Altered by Acid
Tabetic crisis	1	..	0
Acute cholecystitis	4	..	0
Chronic cholecystitis and cholelithiasis	1	0	..
Cholangeitis with jaundice	1	..	0
Subacute appendicitis	1	..	0
Acute enteritis	1	0	..
Subacute suppurative colitis	1	0	..
Functional bowel distress	2	0	..
Tuberculous peritonitis	2	..	0
Tuberculous peritonitis and cirrhosis of the liver	1	..	0

The first protocol again illustrates the production of pain by hydrochloric acid, and later its production by solutions of sulphuric and acetic acid. In the second, pain is produced in four minutes by the injection of gastric juice with a free acidity of 96; but when the acidity is lowered to 6, the latent period is prolonged to fifteen minutes, and then the free acidity is found to have risen to thirty-three. The injection of tenth normal sodium hydroxide brought on distress immediately. It lasted thirteen minutes and then disappeared spontaneously as the gastric secretion reduced the alkalinity. A summary of the results obtained with these different solutions is shown in table 4.

THE EFFECT OF THE ACID INJECTIONS IN OTHER ABDOMINAL CONDITIONS

The mechanism of pain in carcinoma of the stomach is to be discussed in detail later. The introduction of 0.5 per cent hydrochloric acid in the manner described, however, did produce pain nineteen times in eight different patients. In five other patients, the acid produced only a slight burning or no distress at all.

It was shown in the first table that in persons suffering from diseases not essentially related to the gastro-intestinal tract, the acid injections produced no distress other than slight burning, nausea or vomiting. No especial significance is to be attached to these reactions, therefore. The question arises, however, as to whether or not there are conditions other than those of ulcer and carcinoma in which the patient's typical distress may be produced and relieved at will by means of the acid injections. Was there any evidence of gastric hyperesthesia in abdominal conditions not producing ulcerative lesions of the stomach or duodenum? The conditions studied are listed in table 5. In those in which pain was already present, it was not altered by the injection of the acid; in those in which it was absent, it was not initiated by the injection.

There were five cases in which a diagnosis of peptic ulcer was made, but in which roentgen-ray examination failed to reveal any confirmatory evidence. In these five cases, the typical distress was reproduced nine times. Roentgen-ray examination is not expected to show more than about 90 per cent of ulcers, and hence it is entirely fair to consider these five, comprising only 5.6 per cent of the ulcer cases in which pain was produced by the acid as cases of ulcer without roentgen-ray evidence. The patient's typical distress was produced twice in a case that was considered as a possible syphilis of the stomach, but in which no definite diagnosis was made. Of the six cases in this group, then, in which the acid injections did initiate the patient's typical distress, five may be classed quite fairly as cases of peptic ulcer without roentgen-ray examinations; the sixth patient left the hospital symptom-free without a more definite diagnosis than that of syphilis having been made and with only antisyphilitic treatment having been given.

In this entire series of experiments, there is no definite evidence of gastric hyperesthesia in the absence of an organic lesion of the mucous membrane. The only distress produced by the action of 0.5 per cent hydrochloric acid on an intact gastric mucosa was a slight burning. The rapid entrance of acid into the intestine at times produced nausea, retching and vomiting; occasionally, severe cramps and diarrhea.

COMMENT

In the foregoing pages, it has been shown that the introduction of 0.5 per cent hydrochloric acid solution into normal stomachs may produce either no sensation or one of epigastric burning or warmth. The rapid entrance of acid into the duodenum may produce nausea and vomiting. Flushing of the face and headache have been seen occasionally as the result, apparently, of either chemical or mechanical irritation of the duodenum. In patients afflicted with a gastric or duodenal ulcer which was known to be sensitive to the normal irritant, the injection of 0.5 per cent hydrochloric acid solution produced distress which the patient identified as his typical distress in more than 95 per cent of the tests. This distress was produced and relieved at will by perfectly physiologic concentrations of acid. Spontaneous ulcer distress was relieved similarly by emptying the stomach, and initiated again by reintroduction of the aspirated content. Hence, the gastric content contained an irritant to the pain-producing mechanism. Hydrochloric acid was the only irritant common to the two solutions. Pure gastric juice with a high free acid was an adequate stimulus to the pain-producing mechanism, but gastric juice whose free acidity has been neutralized by alkali was not Hydrochloric acid, therefore, is the irritant common to those different solutions which constituted an adequate stimulus to the pain-producing mechanism. At times, the relationship between the concentration of the acid and the severity of the pain seemed to be an almost quantitative one.

In sufficiently sensitive mechanisms, distress may be produced by the injection of solutions of other chemical irritants, such as sulphuric acid, acetic acid and sodium hydroxide. In all cases, the distress produced is relieved by the removal of the chemical irritant from the stomach or by its neutralization or by both. This evidence further supports the view that the action of hydrochloric acid is that of a chemical irritant.

The latent period is a matter of considerable interest. In duodenal ulcers, it might be explained at times by failure of the pylorus to open. In gastric ulcers, this explanation does not suffice. In very sensitive mechanisms, injection of the acid may produce distress immediately; in less sensitive ones, several minutes may elapse, even an hour or more; and in still less sensitive ones, the latent period may be longer, apparently, than the duration of the test. Similarly, the duration of the pain after removal or neutralization of the irritant may vary. At times it disappears immediately; more frequently it gradually diminishes and completely disappears within thirty minutes, rarely forty minutes. In very sensitive mechanisms, the distress may begin as a severe pain; more frequently it comes on gradually, and then increases in severity more or

less rapidly. As the sensitiveness of the ulcer decreases, the latent period gradually lengthens, the severity of the distress diminishes, the pain threshold rises, and finally it becomes completely insensitive to 600 cc. of 0.5 per cent hydrochloric acid for one and a half hours.

The variable factors on which the production of pain with solutions of hydrochloric acid depends may be enumerated as follows: (1) the sensitiveness of the pain-producing mechanism, (2) the concentration of the acid, (3) the amount of acid used, (4) time, (5) the rate of emptying of the stomach and (6) the rate and amount of the duodenal regurgitation of bile and pancreatic juice.

The severity and duration of the pain depend on these factors also. No definite relationship was found between the severity of the pain and the size or depth of the ulcer. In one case in which excruciating pain was seen, the only lesions found at laparotomy were multiple superficial gastric ulcers, none of which penetrated to the serosa.

The only other condition in which acid injections have been found to give results definitely simulating those obtained with an active peptic ulcer is that of carcinoma of the stomach, which is, of course, the only other common cause of gastric ulceration. No evidence has been obtained that hyperacidity regularly produces distress in the absence of a definite organic lesion.

It cannot be assumed from the foregoing work that hydrochloric acid constitutes the only normal stimulus to the pain-producing mechanism of peptic ulcer. It is conceivable that rarely in complicated ulcers the mechanical irritation of coarse food might be sufficient to produce distress. No evidence for this has been found during the course of the present work. Spontaneous ulcer pain without free acid in the gastric content removed at the time of distress has been seen only once and that in a patient with an extremely sensitive pain-producing mechanism. Occasionally, ulcer pain has been seen as the result of external mechanical traumatism to the pain-producing mechanism. The rôle of muscle tension in the distress initiated by hydrochloric acid, and its rôle as a direct mechanical irritant of the pain-producing mechanism, will be considered in the next section.

CONCLUSIONS

1. Typical ulcer distress can be initiated in ulcer patients under suitable conditions by: (*a*) the reinjection of the gruel obtained at the time of distress, (*b*) solutions of hydrochloric acid of similar concentrations (and therefore entirely physiologic) or by stronger solutions, (*c*) solutions of sulphuric and acetic acids and of sodium hydroxide.

2. Such distress is not produced in normal stomachs by similar injections.

3. Distress so produced is relieved by neutralization of the chemical irritant, or by partial removal of the irritant and neutralization of the remainder.

4. Hydrochloric acid is the irritant normally present in the gastric content which constitutes an adequate stimulus to the pain-producing mechanism of a sensitive peptic ulcer.

5. The distress of gastric carcinoma can be similarly induced at times.

6. The distress typical of the other abdominal conditions studied has not been induced by acid injections up to the present time, or, if already present, it has not been altered by them.

7. No evidence has been obtained of hyperesthesia of the gastric mucous membrane, or of pain as the result of hyperchlorhydria with an intact gastric and duodenal mucosa.

CHRONIC BILIARY TRACT DISEASE

THE DIAGNOSTIC CRITERIA *

JOHN G. MATEER, M.D.
AND
W. STUART HENDERSON, M.B.
DETROIT

INTRODUCTION

The refinement of gall tract diagnosis in the last decade represents one of the most fascinating pages in the history of modern medicine. The contributions of Lyon,[1] Smithies,[2] George,[3] Graham,[4] Bernheim,[5] van den Bergh [6] and others are particularly noteworthy. Previous to ten years ago, the diagnosis of chronic gall tract disease was almost wholly dependent on clinical acumen in evaluating various symptom complexes and objective physical findings. Even now the clinical findings are of first importance, not only in furnishing evidence of pathologic morphology of the gall tract, but also in affording the indispensable key to a correct functional diagnosis or evaluation of the patients' gastro-intestinal symptoms. At the same time, in the suspected, borderline cases the clinical diagnosis can now be confirmed and further elaborated and refined, by cholecystography, other types of roentgen-ray evidence, transduodenal biliary drainage, and quantitative determination of the serum bilirubin.

This article is based, for the most part, on a careful analysis of the diagnostic data in relation to the pathologic findings in a series of ninety-four consecutive patients with proved gall tract disease who were operated on. In these ninety-four patients the following pathologic con-

---

* Read before the American Congress of Physicians, Detroit, Feb. 23, 1926.

* From the gastro-intestinal division of the medical department, Henry Ford Hospital.

1. Lyon, B. B. V.: Nonsurgical Drainage of the Gall Tract, Philadelphia, Lea and Febiger, 1923.

2. Smithies, F.; Karshner, C. F., and Oleson, R. B.: Nonsurgical Drainage of the Biliary Tract, J. A. M. A. **77**: 2036-2043 (Dec. 24) 1921.

3. George, A. W., and Leonard, R. D.: The Pathological Gallbladder, Annals of Roentgenology, vol. 2, New York, Paul B. Hoeber, 1922.

4. Graham, E. A.; Cole, W. H., and Copher, G. H.: Roentgenological Visualization of the Gallbladder by the Intravenous Injection of Tetrabromphenolphthalein, Ann. Surg. **80**:473-477 (Sept.) 1924; Cholecystography: Oral Administration of Sodium Tetraiodophenolphthalein, J. A. M. A. **85**:953-955 (Sept. 26) 1925.

5. Bernheim, Alice R.: The Icterus Index (A Quantitative Estimation of Bilirubinemia), J. A. M. A. **82**:291-295 (Jan 26) 1924.

6. Van den Bergh, A. A. H.: La recherche de la bilirubine dans le plasma sanguin par la méthode de la reaction diazoique, Presse méd. **29**:441-443 (June 4) 1921; abstr., J. A. M. A. **77**:235 (July 16) 1921.

ditions were found: Forty-one had gallstones, thirty-six (with and without calculi) had chronic cholecystitis with pericystic adhesions, and fifty-three presented chronic cholecystitis without stones or adhesions, thirty-four of the last patients representing early catarrhal cholecystitis.

The majority of the patients having gallbladder studies in this clinic, and presented in this report, are not selected patients referred here for confirmation of diagnosis or operation after the diagnosis of gallbladder disease has been made elsewhere; but rather they represent a fair cross-section of the average variety of patients seen by any internist and many early and borderline cases are included in which the diagnosis of gall tract disease is suspected from the history and physical examination. We have therefore had a favorable opportunity to study the early manifestations of this condition. In this connection it should be emphasized that 36 per cent of the ninety-four patients operated on had *early* chronic cholecystitis.

In order to confirm the accuracy of the patient's history we have, wherever possible, in those cases presenting a history of pain, seen the patient during an attack. However, in the majority it has been necessary to rely on the patient's description of his symptoms. We will devote considerable attention to cholecystography in an effort to aid in the correct evaluation of this new method of diagnosis.

PATHOLOGY

Before considering the diagnostic criteria of chronic gall tract disease, it is important to review the more fundamental facts regarding the pathology of this condition. Although the finding of chronic interstitial hepatitis of varying degrees has been noted by pathologists for many years, its importance as a pathologic and clinical entity has not until recently received the attention deserved. In 1918, Graham [7] in every case of a series of cases of cholecystitis in which operation was performed, demonstrated some degree of hepatitis. This constant association was essentially confirmed by Judd,[8] who also noted the frequent association of varying degrees of pancreatitis with chronic cholecystitis. In 1924 Heyd, Killian and MacNeal [9] demonstrated that varying degrees of hepatitis are associated with appendicitis and pepitc ulcer, as well as with cholecystitis and pancreatitis. A piece of liver was excised for microscopic study from patients who were found at operation to have

7. Graham, E. A.: Hepatitis; a Constant Accompaniment of Cholecystitis, Surg. Gynec. Obst. **26**:521-537 (May) 1918.

8. Judd, E. S.: Relation of the Liver and the Pancreas to Infection of the Gallbladder, J. A. M. A. **77**:197-201 (July 16) 1921.

9. Heyd, C. G.; Killian, J., and MacNeal, W. J.: The Liver and Its Relation to Chronic Abdominal Infection, The Beaumont Lectures, Series III, St. Louis, C. V. Mosby Company, 1924.

cholecystitis, appendicitis, peptic ulcer or other areas of local abdominal infection drained by the portal circulation. By a careful microscopic study of this tissue a tendency toward the development of an acute hepatitis was demonstrated in cases of acute cholecystitis and acute appendicitis. A similar association of chronic hepatitis with chronic gastro-intestinal infections was evidenced by the histologic study of the liver in numerous cases of chronic gallbladder disease, chronic appendicitis and peptic ulcer. In these cases, numerous mononuclear wandering cells were found in the trabeculae of Glisson's capsule, as well as round cell infiltration about the bile ducts, and a definite increase of fibrous tissue within the liver. In many cases this increase of fibrous tissue was evidenced by scarring visible on the exterior of the liver. In certain cases of acute hepatitis, desquamated epithelium and polymorphonuclear cells were seen within the lumen of the intrahepatic bile ducts. Sudler [10] has demonstrated that there are certain lymphatics which carry lymph from the liver to the gallbladder, whereas the direction of flow in a second set of lymphatics is from the gallbladder to the liver. It is therefore anatomically possible for a cholecystitis to develop secondary to chronic infection and inflammation of the liver, and there is much evidence that this is the pathogenesis of chronic cholecystitis in many cases. At the same time, the pathologic studies of Heyd and MacNeal indicate that the various exacerbations of an established chronic cholecystitis tend to produce repeated insults to the liver, resulting in increased hepatic fibrosis. Heyd has noted further that in some cases the hepatitis is quite marked, whereas the degree of gallbladder disease is only slight or moderate. In other cases there is marked involvement of the gallbladder with only a slight hepatitis.

More recently McIndoe and Counsellor,[11] at the Mayo Clinic, have shown, by injecting the bile duct systems of livers removed at necropsy from patients with chronic gallbladder disease, that there was marked dilatation of the larger extrahepatic bile ducts. (In this group of cases there was little or no dilatation of the terminal intrahepatic bile ducts.) The contrast with the appearance of the bile duct system in normal cases was quite striking.

The foregoing convincing pathologic evidence that cholecystitis should be regarded only as a part of a generalized, chronic infection and inflammation of the biliary tract has its clinical manifestation in the not infrequent observation that after cholecystectomy there may be symptoms that are definitely traceable to residual cholangeitis or hepatitis.

---

10. Sudler, M. T.: The Architecture of the Gallbladder, Bull. Johns Hopkins Hosp. **12**:126-129, 1901.

11. McIndoe, A. H., and Counsellor, V. S.: Studies in the Vascular and Biliary Trees of the Liver, read before the Pathological Section of the Federation of American Societies for Experimental Biology, Dec. 28, 1925.

HISTORY

The symptomatology of chronic gall tract disease may be considered under four headings: In the first group are included such systemic symptoms as anorexia, asthenia and loss of weight, and these manifestations may be present in varying combinations and degrees. Since such symptoms are associated with numerous other conditions, they are, of course, not diagnostic, but are of value when considered in connection with other symptoms.

Under the second heading are included the symptoms of various conditions, e. g., arthritis, myositis and neuritis, which suggest the presence of chronic infection, but do not directly call attention to the gall tract.

A third group comprises such reflex symptoms as belching, bloating, heartburn, nausea and vomiting. As pointed out by Alvarez [12] and others, these symptoms are dependent on reflex pylorospasm and reverse peristalsis in the gastroduodenal segment. Such types of epigastric distress are, of course, not pathognomonic of chronic gallbladder disease, since they occur also in association with peptic ulcer, chronic irritable colon (chronic colitis), chronic appendicitis and other gastro-intestinal, as well as certain pelvic and urinary tract, conditions. Epigastric distress is, however, the earliest and most frequent gastro-intestinal symptom in chronic gall tract disease. If carefully analyzed, this symptom is, moreover, of some help in differential diagnosis.

Epigastric distress dependent on chronic gall tract disease involves belching and bloating in the great majority of patients, and a type of bloating which is often very distressing, and only partially relieved by carminatives such as soda. Nausea and heartburn are somewhat less frequently present. Epigastric distress referable to gall tract disease is usually differentiated readily from that of peptic ulcer by the following points. In the first place, it develops, as a rule, during the first hour after the intake of food. In other words, with the exception of occasional patients with an ulcer-like history, gallbladder distress is aggravated rather than relieved by food, and is often especially aggravated by fatty foods, e. g., cream, eggs and fried foods. Unlike ulcer distress, that of gallbladder disease also occurs quite irregularly and without any definite periodicity. Gallbladder distress can usually be differentiated from the epigastric distress referable to chronic colitis or chronic irritable colon by the following points. The former is not so constantly or so strikingly aggravated by constipation and relieved by a bowel movement or passing flatus. It also differs from colon distress in that it is not aggravated by cold drinks, has no tendency to occur particularly in the morning, and has no direct relation to the

12. Alvarez, W. C.: The Mechanics of the Digestive Tract, New York, Paul B. Hoeber, 1922.

patient's nervous condition. The epigastric distress of chronic appendicitis may simulate closely that of gallbladder disease, but in the latter case there is no history of attacks of right lower quadrant pain.

Under the fourth heading of localizing symptoms, pain under the right costal margin is of first importance. This pain may be dull in character or very severe and colicky. Its frequent radiation to the inferior angle of the right scapula has long been recognized as a helpful diagnostic point when present. Less frequently, the pain may be epigastric in location, and may radiate posteriorly to the interscapular region. In some patients, the periodic attacks of severe pain greatly overshadow the epigastric distress, while in others, the pain may be slight or entirely absent and the epigastric distress may be a most annoying symptom.

The character of the pain present has been analyzed in the series of ninety-four consecutive cases in which operation was performed, and its type noted in relation to the degree and type of gallbladder disease found at operation. In the majority of these cases, as noted above, our information regarding the exact character of the pain is based on the patient's description, being obtained in the interval between attacks.

Gallstones were found in exactly two out of every three patients who characterized their pain as being severe. In those cases having typical colic, with sudden onset of extremely intense pain requiring opiates for relief, gallstones were almost always found at operation, although we have observed several patients with definite colic in whom no calculi were found. Among those who described their pain as dull, gallstones were found in only one patient out of four. The severity of pain, and particularly the presence of typical colic, does, therefore, aid greatly in differentiating the cases with and without stones.

Radiation of pain to the region of the inferior angle of the right scapula was noted in 66 per cent of the group of sixty-one patients who had had pain under the right costal margin and who were operated on. Of the forty patients who had this radiation of pain, 55 per cent showed gallstones at operation. Of the 45 per cent with radiation of pain but no calculi, at operation 53 per cent had pericystic adhesions, whereas the other 47 per cent were patients with simple chronic cholecystitis. In analyzing the group of patients with pain starting in the epigastrium and radiating through to the interscapular region, it was found that exactly 50 per cent presented gallstones at operation, whereas the others harbored no calculi. These findings corroborate the opinion expressed by others that the radiation of pain in chronic gallbladder disease, unlike the severity of the pain, is of no real value in differentiating the patients with and without gallstones or pericystic adhesions.

There are, of course, variations from usual locations and radiations of pain in chronic gallbladder disease mentioned in the foregoing. The

pain may start in the region of the right scapula and radiate forward, or occasionally one sees a person with sharply localized pain referred to a small area beneath the right scapula, and with no radiation. Epigastric pain, instead of radiating to the interscapular region, may shift to the right scapular region or to the right costal margin.

In the differential diagnosis of right upper quadrant pain, one should consider first the more common conditions, such as chronic gallbladder disease and chronic irritable colon, and then the less frequent causes, such as anterior reference of right sided kidney pain, chronic appendicitis involving a displaced, adherent appendix, and the infrequent reference of pancreatic pain to this locality. The fact that chronic irritable colon is a common cause of right upper quadrant pain should be emphasized, as there are frequent errors in the diagnosis of chronic gallbladder disease resulting from the fact that colon conditions are not always given due consideration in this differential diagnosis. Colon pain, fortunately, has numerous features that tend to characterize it as such: for example, its tendency to localize at times in any one of the four abdominal quadrants, but at other times to shift from one quadrant to another; its tendency to be aggravated by coarse vegetables, fruits, cold drinks, constipation and nervous upsets, and to be relieved by fasting or by a bland diet, by the application of heat, by proper regulation of the bowels, or by rest, and finally, by the fact that it usually occurs in transient, cramplike paroxysms, lasting only a short time, whereas in gallbladder attacks the pain may persist rather steadily for a period of several hours.

Twenty-two per cent of the ninety-four cases in which operation was done presented either a definite history of at least one period of jaundice or afforded definite evidence of jaundice at the time of examination, and the history of a periodic "sallow" or "muddy" complexion was frequently elicited. Conversely, in any large group of unselected patients with jaundice, about 55 per cent will be found to have chronic gall tract disease, with either a hepatitis or a stone in the common bile duct as the underlying basis. Determination of the exact cause of jaundice usually involves, in addition to a careful evaluation of the clinical findings, observations on the serum bilirubin, other studies of the blood, examinations of the urine and stool, and duodenobiliary drainage—or at least attempts to obtain bile in this manner. The classical clinical picture in common duct stone of colic, jaundice and evidence of sepsis needs no elaboration.

PHYSICAL EXAMINATION

The evidence of chronic gall tract disease afforded by physical examination must be obtained and interpreted with care, but is of much value. Definite tenderness in the gallbladder region on palpation upward under the right costal margin is a most valuable sign. The importance of differentiating between gallbladder and colon tenderness in the right

upper quadrant should be emphasized. With the patient in the reclining position, this differentiation is frequently difficult or impossible. It is therefore always advisable to examine a patient with suspected gallbladder disease in the sitting posture. This allows the transverse colon to drop down and away from the costal margin, and at the same time facilitates upward palpation of the liver edge and gallbladder region. It is advisable during such examination to have the patient lean slightly forward, breathe through the mouth, and relax the abdominal muscles. The fact that gallbladder and colon conditions frequently coexist adds to the importance of this method of examination. It is a well recognized fact that involuntary increased muscle resistance during palpation is a more reliable indication of significant tenderness than the mere statement of the patient that pain or distress is felt during palpation.

Repeated abdominal examinations during a period of observation are often necessary before gallbladder tenderness is elicited This fact is, of course, due to the characteristic exacerbations and remissions in the life cycle of chronic gall tract disease. Definite tenderness may be demonstrated in the gallbladder region during or immediately after a gallstone attack, whereas a few hours later it may be impossible to elicit any tenderness in this locality. In 85 per cent of the ninety-four cases in which operation was performed gallbladder tenderness was elicited at one time or another before operation.

The finding of a definite tumor in the gallbladder region, the characteristics of which identify it as the gallbladder, indicates one of four conditions: (1) empyema; (2) hydrops of the gallbladder, usually associated with a stone in the cystic duct; (3) carcinoma, or (4) occasionally, a gallbladder filled with stones which can be palpated through a lax abdominal wall. We have twice seen the latter finding confirmed at operation.

The incidence and evaluation of the finding of jaundice has been discussed under a previous heading.

QUANTITATIVE SERUM BILIRUBIN DETERMINATION

The value of a quantitative serum bilirubin determination in demonstrating a latent jaundice in gall tract disease is now generally recognized. The two methods that are apparently in widest use at the present time are: (1) the quantitative *indirect* van den Bergh method,[6] as modified by Thannhauser and Andersen[13] and advocated by Greene, Snell and Walters,[14] and (2), the icterus index method as described by

13. Thannhauser, J. S., and Andersen, E.: Methodik der quantitativen Bilirubinbestimmung im menschlichen Serum, Deutsches Arch. f. klin. Med. **137**:179-186 (Aug.) 1921; abstr., J. A. M. A. **77**:1292 (Oct. 15) 1921.

14. Greene, C. H.; Snell, A. M., and Walters, W.: A Survey of Tests for Hepatic Function, Arch. Int. Med. **36**:248-272 (Aug. 15) 1925.

Bernheim.[5] Because of its simplicity, the latter method has had a rather wide clinical use. It has, however, two important limitations, due to the fact that it is based on the hypothesis that the yellow in the serum is a quantitative index to the amount of bilirubin present. In this connection, Bernheim recognized the necessity of being very careful to avoid any trauma of the red blood cells, which may result in hemolysis with misleading discoloration of the serum. She also recognized the necessity of eliminating from the patient's diet pigment containing foods, such as carrots, which might and do produce discoloration of the serum. If these two pitfalls are kept in mind in using this method, satisfactory results can be obtained in the majority of patients. There can be no doubt, however, that the data obtained will be more uniformly reliable if the quantitative indirect van den Bergh method, which is a specific test for bilirubin, is used. We have frequently used both methods, checking the results of one with those of the other. In addition, the *direct* van den Bergh reaction has been carried out in those cases of clinical jaundice in which there has been some doubt as to the underlying cause or type of jaundice present.

A quantitative serum bilirubin determination is indicated particularly in cases of suspected gall tract disease in which there is still some doubt about the diagnosis after the other diagnostic evidence has been obtained. Such a determination should be carried out, however, in every suspected case of gall tract disease, because it frequently adds to the total diagnosis by affording evidence of hepatitis. Another important use of this procedure consists in the frequent determination of the serum bilirubin during the observation of a frankly jaundiced patient. It is thus possible to obtain early and reliable information as to increase, decrease, or fluctuation in the degree of jaundice, which frequently clarifies the diagnosis of the underlying condition. Furthermore, as emphasized at the Mayo Clinic, valuable information as to the indication for surgical treatment and the best time for operative intervention is obtained in jaundiced cases by following the serum bilirubin until it has reached a stationary level, surgery usually being contraindicated while it is increasing or decreasing.

ROENTGEN-RAY STUDIES

(*a*) *Earlier Methods.*—Until the introduction by Graham of his ingenious method for studying directly the morphology and physiology of the gallbladder, the roentgen-ray methods used in gallbladder diagnosis afforded valuable information in a certain number of cases; but there were too many instances in which they made either no contribution to the diagnosis, or else afforded only evidence of an indirect and inconclusive nature. The two sources[8] of roentgen-ray evidence then available were: (1) simple gallbladder plates, which in some cases revealed

stone shadows and in others a visible gallbladder shadow, and (2) a barium meal roentgen-ray series, which, in some instances, disclose a concave "pressure defect" (usually involving the duodenal bulb), and in others evidence of right upper quadrant adhesions with displacement and a tendency to fixation of the distal antrum, proximal duodenum, or proximal colon.

In the indirect roentgen-ray evidence obtained from a barium meal [15] examination, the finding of a definite, concave pressure defect is, we believe, often, although not always, due to gallbladder pressure. We have seen a few patients with a pressure defect who presented at operation a gallbladder firmly attached by adhesions to the first portion of the duodenum, and other patients in whom a cluster of gallstones in the stomach plates nestled in the concavity of a duodenal pressure defect. We are not convinced, however, that pressure of the gallbladder on the duodenum necessarily means cholecystic disease; nor does such pressure, when present, give any indication as to the degree of disease present. Fifty-seven of the ninety-four patients operated on for gall tract disease received a barium meal examination, and 14 per cent (eight cases) presented a persistent concavity involving the first portion of the duodenum. Barium meal evidence of right upper quadrant adhesions, involving the duodenum or proximal colon, is of considerable value when definitely present, although care must be exercised in its evaluation.

The direct evidence obtained from simple gallbladder plates is summarized in table 1. This includes an analysis of the findings in the simple gallbladder plates and cholecystograms of the fifty-eight patients operated on for gall tract disease who were studied by both methods. In this group gallstone shadows were noted in 17.9 per cent of the patients having gallstones at operation. In the total group of ninety-four patients operated on, gallstone shadows were seen in 22 per cent of the gallstone cases. As regards the identification and interpretation of a "visible gallbladder shadow," cholecystography has taught us that in some preliminary gallbladder plates a shadow that apparently represents a gallbladder shadow may be located in a very different position from the known gallbladder shadow in the cholecystograms. We feel, therefore, that, whenever possible, the identification of a "visible gallbladder shadow" should be postponed until the position of the shadow in question can be compared with the known gallbladder shadow in the cholecystograms. If the gallbladder fails to fill with the dye, such comparison is, of course, impossible. In this connection, some shadows can be independently identified as visible gallbladder shadows with somewhat more confidence than others. A visible gallbladder shadow was noted

15. Burnham, M. P.: Importance of Indirect Roentgen Findings in Chronic Infection of the Biliary Ducts and Gallbladder, Am. J. Roentgenol. **10**:105-112 (Feb.) 1923.

in 10.3 per cent of the fifty-eight pathologic cases. In five of these six cases the position of the shadow coincided with the position of the gallbladder shadow in the cholecystograms. In the sixth case the gallbladder was not visualized in the cholecystograms, but the shadow in the gallbladder plates was quite convincing.

TABLE 1.—*Analysis of Cholecystograms and Preliminary Gallbladder Roentgenograms of Sixty-four Patients that Were Operated on* *

	Number of Cases Presenting Roentgen-Ray Sign	Percentage of 58 Pathologic Cases Presenting Roentgen-Ray Sign	Pathologic Findings at Operation, Number of Cases	Percentage of Correct Roentgen-Ray Diagnoses	Percentage of patients Receiving Dye Orally
I. Cholecystograms					
No gallbladder shadow..	27	43.1 (25 cases)	(a) Cholecystitis 8 (b) Gallstones... 17 (c) No disease... 2	92.6	89
Faint gallbladder shadow (with or without associated mottling of shadows or loss of sequence)	13	20.7 (12 cases)	(a) Cholecystitis 8 (b) Gallstones... 4 (c) No disease... 1	92.3	77
Stasis (appreciable degree, with only slight contraction of gallbladder shadow)	4	6.9 (4 cases)	(a) Catarrhal cholecystitis 4	100	50
Negative stone shadows..	5	8.6 (18% of gallstone cases)	(a) Gallstones... 5	100	100
Positive stone shadows † (gallbladder not visualized with dye)	4	6.9 (14.3% of gallstone cases)	(a) Gallstones... 4	100	100
Irregularity (angular) in contour of gallbladder shadow	9	15.5	(a) Chronic cholecystitis with pericystic adhesions..... 8 (b) Gallstones... 1	100	89
Normal shadows and sequence	7	6.9 (4 pathologic cases)	(a) No disease... 3 (b) Cholecystitis 3 (c) Gallstones... 1 ‡	42.9§	42.9
II. Gallbladder roentgenograms					
Gallstone shadows	5	8.6 (17.9% of gallstone cases)	(a) Gallstones... 5	100	
Visible gallbladder shadow (described in context)	6	10.3	(a) Cholecystitis 2 (b) Gallstones... 4	100 ‖	
Total cases with either gallstone shadows or visible gallbladder shadow	9	15.5 (32.1% of gallstone cases)	(a) Cholecystitis 2 (b) Gallstones... 7	100	

* Fifty-eight of these patients presented at operation definite evidence of chronic gallbladder disease, twenty-eight having gallstones. The oral method of cholecystography was used in 80 per cent (fifty-one) of these cases.

† Not included under specific cholecystographic evidence, because also obtained from preliminary gallbladder plates.

‡ Although a normal gallbladder shadow was seen in the second set of cholecystograms, no gallbladder shadow was seen in the first cholecystograms of this patient. (The sequence of shadows is therefore not entirely normal in this case.)

§ This percentage figure would doubtless be much higher in a group of cases without definite clinical evidence of cholecystitis.

‖ The error involved in those cases with an apparently visible gallbladder shadow, the position of which did not coincide with that of the gallbladder in the cholecystograms, is not included in this figure.

(*b*) *Cholecystography.*—Cholecystography, first presented to the medical profession by Graham in 1924, at present justifies the enthusiasm noted at the time of its introduction. During the last year we have carried out cholecystography in 590 cases of suspected gallbladder disease, and during this time we have been much interested in the evolution of

the method, both as to the dye used and the method of administration. A careful analysis of the patient's reactions following various methods, and also of the findings in the cholecystograms, has afforded interesting results and conclusions.

1. Evolution of Method: After carrying out the intravenous administration of sodium tetrabromphenolphthalein in forty-seven cases, this method was entirely discarded because a marked circulatory reaction was obtained in 17 per cent of the patients, with a transient state of collapse in 6 per cent. It should be noted, however, that there were no unfavorable end-results. With the demonstration by Whitaker and Milliken [16] that sodium tetraiodophenolphthalein is no more toxic per unit weight than sodium tetrabromphenolphthalein, and that a smaller quantity of the iodine dye gives equally satisfactory shadows, cholecystography was carried out on seventy patients to whom the iodine rather than the bromine salt was given intravenously. By this change of method, circulatory reactions were reduced from 17 to 1.4 per cent. Furthermore, 60 per cent of the patients had no reaction of any sort. Several of the latter, however, did develop rather extensive thromboses of the arm veins. In view of this fact, and since any intravenous method is time consuming and necessitates hospitalization of the patient, we have now practically given up the intravenous method. Administration of the dye through the duodenal tube was carried out in a few cases, but was discontinued as soon as it was learned that most of these patients had vomiting, and some circulatory, reactions, apparently due to the rapid absorption of the dye. Since the publication of the first oral method by Menees and Robinson,[17] we have administered the dye orally to 463 patients. Menees' method of administering the dye emulsified in olive oil and in gelatin capsules that have been exposed to formaldehyde has proved most satisfactory. Oral administration of the dye in tablets coated with phenol salicylate was discarded because diarrhea occurred three times as frequently as with the gelatin capsules that had been exposed to formaldehyde. With the oral method we have seen no circulatory reactions. In the relatively small group of cases with suggestive but not definite evidence of cholecystic disease in the cholecystograms, and no definite clinical evidence, it seems preferable to repeat the oral method and rely on the constancy of the findings, rather than resort to the intravenous administration for confirmation. Ques-

16. Whitaker, L. R., and Milliken, G.: Comparison of Sodium Tetrabromphenolphthalein with Sodium Tetraiodophenolphthalein in Gallbladder Radiography, Surg. Gynec. Obst. **40**:17-23 (Jan.) 1925.

17. Menees, T. O., and Robinson, H. C.: Oral Administration of Sodium Tetrabromphenolphthalein; Preliminary Report, Am. J. Roentgenol. **13**:368-369 (April) 1925; Oral Administration of Tetraiodophenolphthalein for Cholecystography, Radiology **5**:211-221 (Sept.) 1925.

tionable points have thus usually been cleared up in a satisfactory manner. No appreciable difference has been noted in the incidence of local gastro-intestinal disturbances in comparing the eighteen patients who received the bromine salt orally with the 445 patients who were given the iodine salt by mouth. Preference has been accorded the iodine salt because, as noted above, the toxicity of the dose necessary to produce satisfactory shadows is much less than that of the bromine salt.

2. Present Method of Administration of Dye and Rationale: The oral method followed at the present time and its rationale are as follows: Ten-grain (0.6 Gm.) gelatin capsules are exposed under a bell jar to formaldehyde fumes, as recommended by Menees.[17] Exposure for a period of six hours is much more satisfactory than the longer period of twenty-four hours first used. With this change in technic the capsules are more promptly digested in the intestine. The capsules should be freshly exposed to formaldehyde every several days, as old capsules exposed to formaldehyde seem to digest less promptly in the intestine. We have used capsules exposed to formaldehyde rather than those coated with keratin because in vitro experiments, in which artificial gastric juice was used, have convinced us that capsules exposed to formaldehyde for six hours were somewhat more resistant to gastric digestion than those with keratin coating. It is important to note that the main objection raised against the oral method is the possibility that the dye capsules may be only partially digested and the dye incompletely absorbed. That this is not a valid practical objection, if a proper technic is used, is apparent from the following facts:

1. The stools of fifty consecutive patients, who had received dye capsules exposed to formaldehyde for six hours, were sieved, all stool specimens having been saved over a period of thirty-six hours after administration of the dye; but not a single undigested capsule was found. (Loss of dye by the vomiting of capsules occurs only rarely, and is readily detected when it does occur, if the patient has been properly instructed.)

2. In a group of cases large serial films taken every hour after oral administration have shown that the dye capsules begin to break down within two hours, and digestion of the capsules is usually complete within eight hours.

3. With the technic now used no undigested capsules have been found in the large films of the abdomen, taken routinely when the twelve hour cholecystograms are obtained, and those cases presenting small quantities of disseminated, unabsorbed dye in these films can be noted in relation to the interpretation of the cholecystograms.

4. As noted below, the entrance of the dye into the gallbladder and the visibility of the gallbladder shadows have been essentially as satis-

factory with the oral as with the intravenous method, although the shadows are, of course, less dense.

Into each capsule exposed to formaldehyde 0.5 Gm. of sodium tetraiodophenolphthalein is introduced, emulsified in a small quantity of olive oil. The two parts of the capsule are then sealed with melted gelatin. We agree with Stewart [18] that it is important to use a fresh preparation of the dye. As regards the quantity of the iodine salt to be given, 0.06 Gm. per kilogram of body weight (with minimum and maximum doses of 2.5 and 5.5 Gm., respectively) has been found to produce satisfactory shadows. With this dose of fresh dye, nausea and vomiting occur in only a small percentage of patients. Rather than give a larger number of smaller capsules in order to maintain more accurately the exact proportion between body weight and amount of dye given, it has been more satisfactory, on the whole, to administer the larger dose per capsule referred to above, and to give from five to eleven capsules in divided doses at 8 and 8:30 p. m., the patient having previously eaten a small meal at 5 p. m. The patient is instructed to retire before taking the capsules. One dram of sodium bicarbonate is given at 8 p. m., and again at 8:30 p. m., in order to prevent precipitation of the dye within the capsule by the entrance of hydrochloric acid.

3. Time Intervals Observed in Taking Cholecystograms: On the day following ingestion of the dye, twelve hour plates are taken at 8:30 a. m., sixteen hour plates at 12:30 or 1 p. m., and twenty hour plates at 4:30 p. m. A final set of thirty-six hour plates have been taken at 8:30 a. m. of the following day. After taking the dye capsules the patient fasts until after the sixteenth hour plates are obtained. A small meal, including beef broth and cream, is then given in order to induce as much emptying of the gallbladder as possible before the twenty hour plates are taken. Subsequently, the patient eats the usual evening meal, and breakfast the following morning. Immediately after the twelve hour cholecystograms and the large control plate of the entire abdominal cavity have been taken, the patient is given a cleansing enema in preparation for the sixteen and twenty hour plates. A second enema is given on the morning of the following day preparatory to the thirty-six hour films. As noted below, we feel that there is doubt as to the value and interpretation of the thirty-six hour plates, and we are planning to discontinue them.

4. Signs and Their Evaluation: Of the 590 patients studied by cholecystography, sixty-four have, up to date, come to operation, and the operative findings have been compared with the evidence in the

18. Menees and Robinson (footnote 17) second reference, discussion by W. H. Stewart.

cholecystograms. Fifty-eight of these patients presented definite evidence of chronic gallbladder disease, twenty-eight having gallstones. (Of the ninety-four patients operated on for gall tract disease who have been analyzed from the standpoint of clinical findings, the last fifty-eight patients had cholecystography.) The gallbladder appeared normal at operation in the other six cases, and was not removed. Eighty per cent of the patients operated on received the dye orally; and the results are, therefore, mainly an index to the value of the oral method. The incidence and reliability of the various cholecystographic signs in these sixty-four cases are indicated in detail in table 1. By referring to table 2 it will be noted that the positive cholecystographic evidence is considered under the two headings of indirect and direct evidence.

The sign which occurs with greatest frequency, and which is more reliable than any of the other indirect signs, is failure to visualize a gallbladder shadow in any of the serial cholecystograms. Forty-three per cent (twenty-seven of the sixty-four cases) presented this sign. Gallstones were found at operation in 63 per cent (seventeen) of these cases with no visualization of the gallbladder. (In one case carcinoma of the gallbladder was found in addition to calculi.) Eight of these cases had a cholecystitis without stones, and in two cases the gallbladder appeared normal at operation, and was not removed. In the last two cases the operation was performed, in one instance, for pyloric obstruction, and in the other for chronic appendicitis, the gallbladder being explored because of the roentgen-ray observations. The percentage of correct diagnosis with this sign was therefore 92.6 per cent. Twenty-four of the twenty-seven patients presenting this sign received the dye orally. Impaired ability of the gallbladder wall to concentrate the solid contents of the bile would seem frequently to be the important factor in the failure of the gallbladder to become visible with the dye. In other cases, cystic duct obstruction or obliteration of the gallbladder lumen with calculi is doubtless the cause.

A second, less frequent, indirect sign of value consists in persistent faintness of the gallbladder shadow in the serial cholecystograms. Although with the oral method the interpretation of faintness of the shadow is not so easy and unequivocal as with the intravenous method, nevertheless we agree with the opinion expressed by Carman [19] and others that this sign is of considerable value, provided uniform technic is followed and if the following points are considered in this technic: (1) careful notation of any dye lost; (2) consideration of thickness of the patient's abdominal wall, and (3) variation in the dosage of the dye depending on the patient's weight. If under these conditions the faint-

19. Carman, R. D.: Cholecystography in Its Application to the Diagnosis of Cholecystic Disease, Minnesota Med. **8**:707-712 (Dec.) 1925.

ness is definite and marked, and particularly if some other indirect sign, such as delayed visualization of the gallbladder, failure of the shadow to contract, appreciable stasis of the dye or mottling of the shadow, is present, one is justified in attaching diagnostic value to the observation. This sign was present in 20.7 per cent (thirteen) of the sixty-four patients. In 92.3 per cent, or twelve of these patients, some degree of chronic cholecystitis (with or without stones) was found. In ten of these thirteen patients there was not only faint filling but also definite mottling of the gallbladder shadow, which did not give the impression of superimposed gas in the intestine. In ten of the thirteen patients the oral method was used.

The third indirect sign consists of delayed emptying of the gallbladder, which, when marked, and particularly when associated with only slight contraction of the shadow, is of very suggestive diagnostic value. If, on the other hand, there is good contractility of the shadow and only a relatively small amount of dye is visualized in the third set of cholecystograms, one is not justified in attaching any definite significance to the observation. As regards the interpretation of the thirty-six hour plates in relation to stasis, reabsorption of the dye constitutes a possible source of error. We have noted several cases in which the gallbladder shadow had entirely disappeared in the twenty-four hour plates, but was readily visualized again in the thirty-six hour films Four of the cases in which operation was performed presented marked stasis of the dye with only slight contraction of the shadow, and in all of these a catarrhal cholecystitis was found at operation. Appreciable stasis of the dye has been noted in a much larger number of cases that have not come to operation. A study of further operated cases is necessary before this sign can be satisfactorily evaluated. The fourth indirect sign, *delayed* filling or visualization of the gallbladder, also deserves further study as to its value.

There are two *direct* signs in cholecystography which are of definite diagnostic value when present, viz., (1) negative gallstones shadows, and (2) angular irregularity in the contour of the gallbladder shadow. A total of 24.1 per cent (fourteen) of the fifty-eight pathologic cases presented definite evidence of one or the other of these two direct signs. In 8.6 per cent of these cases in which operation was done, and in a larger number of cases in which operation was not yet performed, areas of negative density were noted within the gallbladder shadow, the character of which definitely identified them as gallstone shadows. In none of these cases were gallstone shadows apparent in the preliminary gallbladder plates. On the other hand, the heavier, calcified type of stone, which reveals itself in the simple gallbladder plates, may be entirely concealed in the cholecystograms if the dye enters the gallbladder and is

concentrated. In four of the five cases in this series which showed positive gallstone shadows in the preliminary gallbladder plates, the gallbladder failed to fill with the dye and the positive stone shadows therefore persisted in the cholecystograms (tables 1 and 2).

Angular irregularity in the contour of the gallbladder shadow may be considered under two headings. In four of the cases in which operation was performed there was, in the cholecystograms, a striking and persistent displacement of the lower pole of the gallbladder. This involved a marked and angular flexion of the fundus on the neck of the viscus. In all four cases the preoperative diagnosis of pericystic

TABLE 2.—*Deductions from Table* 1.

	Total Number of Cases	Cases Presenting Gallbladder Disease	Cases With No Disease at Operation	Percentage of Correct Diagnoses	Percentage of Error in Diagnosis
Cases presenting positive (direct or indirect) evidence with cholecystography	57	54	3	94.7	5.3
Cases presenting normal shadows with cholecystography	7	4	3	42.9 *	57.1
Total cases in which operation was performed studied by cholecystography	64	58	6	89.1 (57 cases) (positive and negative diagnosis)	10.9 (positive and negative error)
Percentage of positive error in diagnosis by cholecystography in total cases studied					4.7 (3 of 64 cases)
Percentage of negative error in diagnosis by cholecystography in total cases studied					6.2 (4 of 64 cases)

	Total Number of Cases	Percentage of Total (58) Pathologic Cases
Pathologic cases with direct evidence in cholecystograms of chronic gallbladder disease, and no evidence in preliminary gallbladder roentgenograms	14	24.1
Pathologic cases with either direct evidence or persistent absence of shadow, and no evidence in preliminary gallbladder plates	30 (16 "no shadow" cases)	51.7
Pathologic cases with some type of direct or indirect evidence of disease in cholecystograms (table 1) and no evidence in preliminary gallbladder roentgenograms	45	77.6

* This percentage figure would doubtless be much higher in a group of cases without definite clinical evidence of cholecystitis.

adhesions was confirmed at operation. It seems likely that further experience will confirm the reliability of this sign. This type of angular deviation in the long axis of the gallbladder should be differentiated from the rather frequent lateral or medial displacement without angular deviation. The latter finding has no definite pathologic significance.

In five of the cases in which operation was performed an irregularity in the gallbladder contour was noted, without any deviation of its long axis. In four of these five cases dense pericystic adhesions were found, without gallstones. In the fifth case gallstones were found, without pericystic adhesions.

To summarize, eight of the nine cases with irregular contour of the gallbladder shadow presented pericystic adhesions as the cause of this

finding, whereas the ninth patient had gallstones. This sign was present in 30 per cent of the patients who showed pericystic adhesions at operation.

It is finally important to determine the significance of entirely normal findings in the cholecystograms. Do such findings have a value in ruling out cholecystic disease? Seven patients were operated on whose cholecystograms indicated normal filling, emptying, density and contour, except that one case showed evidence of delayed filling or visualization of the gallbladder. Four of these patients had convincing clinical evidence of cholecystic disease. Three of these four patients were found at operation to have a catarrhal cholecystitis, and the fourth patient (with delayed filling, but a normal shadow) had gallstones. All were relieved of symptoms following cholecystectomy. These cases prove definitely that normal observations with cholecystography do not rule out chronic gallbladder disease, and should not be accorded negative value in the presence of positive clinical data. Normal cholecystograms, however, make unlikely the presence of marked gallbladder disease and necessitate convincing clinical evidence to justify a definite diagnosis of cholecystitis. Other writers have reported but few cases of gallstones or marked thickening of the gallbladder wall at operation associated with normal cholecystography. In view of the fact that very early cases of chronic cholecystitis may show only slight deviation from normal in the physiology and gross anatomy of the gallbladder, and may yet present convincing clinical evidence of disease, it seems probable that this group of cases will constitute the most important limitation of cholecystography. It seems probable, however, that by giving more consideration to the concentrating function of the gallbladder, as evidenced by the indirect cholecystographic signs and the sequence of the shadows, that a larger percentage of comparatively early cases of cholecystitis will be diagnosed by this method. The other three patients operated on who had normal cholecystograms had no clinical evidence of gallbladder disease, and were operated on for some other abdominal condition. These three gallbladders appeared normal.

In summarizing the value of cholecystography, it is noted that this method afforded correct evidence as to the presence of chronic gallbladder disease in 89.1 per cent of this group of sixty-four cases in which operation was performed (table 2). The percentage of positive error in diagnosis was 4.7, whereas the negative error was 6.2 per cent.

In estimating the value of cholecystography as an additional aid to the roentgen-ray diagnosis of gallbladder disease, it is interesting to note that, of the fifty-eight pathologic cases, 51.7 per cent failed to show evidence of gallbladder disease in the preliminary gallbladder plates, and yet showed either direct cholecystographic evidence or persistent

failure of the gallbladder to be visualized in the cholecystograms. This percentage of cases is further increased if all cholecystographic evidence is included.

Later review of a larger group of cases in which operation was performed may reduce somewhat the percentage of correct diagnosis with this method, but there can be no doubt that the percentage will still be high. It will be interesting to obtain an operative check on cholecystography which will include a larger number of borderline cases that lack convincing clinical evidence of gallbladder disease. It will be in this group of cases that cholecystography will receive the most severe test as to its limitations.

DUODENOBILIARY DRAINAGE

Since the introduction by Lyon [1] of duodenobiliary drainage as a method of value in gall tract diagnosis, it has been employed extensively as a diagnostic measure, and also as a therapeutic measure in selected cases. As a result, much has been learned about its value and limitations. The technic of the method is well known to all. The importance of prompt examination of the bile specimens is also now generally appreciated.

Rather than enter on a discussion of some of the points which are still controversial, we wish to direct attention to the conclusions arrived at concerning its practical value and limitations, and to the observations on which these conclusions are based. This consideration will be limited mainly to the significance of three microscopic findings in the bile: (1) bile stained clumps of pus cells; (2) bile stained colonies of bacteria, and (3) cholesterin or calcium crystals.

In the interpretation of these cytologic elements found in the bile obtained from the duodenum, it has seemed important, in the first place, to determine whether in each individual case the material might have come from the mouth, stomach or duodenum; second, whether the evidence indicates that it does come from some part of the bile tract, and if so, in the third place, whether it originates from the gallbladder or from some part of the bile duct system.

Anyone who has examined many bile specimens from patients with suspected gall tract disease will appreciate the fact that small mucous flecks containing bile stained pus cells are frequently found. The importance of determining the point of origin of these cells depends on the recognized fact that pus cells indicate irritation and inflammation at the site of their liberation. The possibility of focal infection in the mouth, nose or throat, or of infection of the gastric mucosa, has been considered in each case as a possible source for the pus cells found in the bile. In other words, it is conceivable that pus cells may enter the duodenum from the stomach, and there become bile stained.

That neither the mouth, stomach nor duodenum are the usual source of the bile stained pus cells found in the recovered bile is evidenced by the following facts: In the first place, it is recognized that the pus cells in the fasting gastric contents are very frequently associated with squamous mouth epithelium, and have originated from focal infection in the mouth, nose and throat. In view of this fact, if the pus cells that originate in the mouth and throat and pass into the stomach were the common source for the pus cells found in the bile, we should expect to find the same association of squamous mouth epithelium with the pus cells in the bile as with those found in the stomach. This is certainly not the case. In fact, squamous epithelium is rarely found in the microscopic examination of either the bile or duodenal contents. It is evidently digested for the most part in the stomach, along with at least many of the pus cells. The type of epithelium that does occur rather frequently in the bile, and in association with the bile stained pus cells, consists of the fans of characteristic, high columnar bile duct epithelium described by Lyon. The fact that the shape and size, as well as the position of the nuclei, of these cells are quite different from the morphology of gastric epithelium, and also different from duodenal epithelium, is a convincing argument against the hypothesis that the pus cells found in the bile originate in the stomach or duodenum.

In the second place, one frequently fails to find pus cells in the control fasting gastric contents, in the washings from the stomach, or in the duodenal contents, and yet may find an abundance of bile stained pus cells in two or three consecutive bile specimens. Conversely, one frequently finds numerous pus cells in the fasting gastric contents, and yet no pus cells in the duodenal contents or in any of the bile specimens. In other words, there is no constant tendency to coexistence of pus cells in the gastric contents and pus cells in the duodenal contents or bile.

In the third place, bile stained pus cells were found before operation in the bile of 51 per cent of our series of ninety-seven cases of chronic gall tract disease in which operation was performed whereas pus cells were found in the duodenal contents in only 10 per cent of the same group.

Other observations could be cited to support the belief that the bile stained pus cells originate, at least in many cases, from some part of the biliary tract. Specimens of bile which contain an admixture of gastric contents, and in which the interpretation of the microscopic findings should be particularly critical, are easily identified, as a rule, by the turbid layers of bile salts, precipitated by spurts of acid gastric juice. As a safeguard against error of interpretation in the individual case, a microscopic examination of the fasting gastric and duodenal

contents should always be carried out as a control for the interpretation of the bile examination.

Although the significance of the bile cultures is still a matter of controversy, the microscopic observation of numerous, bile stained colonies of bacteria in the bile of patients whose gastric and duodenal contents fail to show bacteria constitutes quite convincing evidence of gall tract infection. *Colonization* of bile stained bacteria, as emphasized by Lyon, points to the actual growth and multiplication of organisms rather than simply to bacteria in transit.

In those cases which present convincing evidence that the bile stained pus cells or colonies of bacteria originate from some part of the biliary tract, we have been interested in determining whether this evidence of inflammation and infection comes from the gallbladder or from some part of the bile duct system. Bile has been aspirated directly from the gallbladder of fifty-four of the ninety-four patients with chronic gall tract disease operated on, and has been examined microscopically. No pus cells or epithelium were found in any of these specimens. This we regard as convincing evidence that the bile stained pus cells previously found in the duodenal bile of 51 per cent of the same group did not come from the gallbladder, but rather from some part of the biliary duct system. This observation also suggests that these bile stained pus cells are probably contributed to the bile as it passes through the lower part of the common bile duct, rather than that they originate in the smaller ducts. For, if the latter were true, one would expect to find bile stained pus cells in the gallbladder bile at operation. To summarize: The observation in the bile of bile stained pus cells and bile stained colonies of bacteria, when other sources have been excluded, affords direct evidence of a chronic cholangeitis (probably involving the common bile duct) and indirect evidence of some degree of cholecystitis.

The other important microscopic observation in the bile is the observation of cholesterin or calcium crystals. Lyon,[1] Einhorn [20] and Jones [21] have emphasized the value of this observation in the bile in the diagnosis of gallstones. Of the fifty-four cases of chronic gall tract disease in which operation was done and the gallbladder bile examined at the time of cholecystectomy, and the results compared with those of the duodenal bile, twenty-three patients had stones in the gallbladder. The gallbladder bile of these patients revealed an abundance of cholesterin crystals in seventeen cases, or 74 per cent. In many of

20. Einhorn, M.: The Importance of the Direct Examination of Bile in the Diagnosis of Gallbladder Lesions, M. J. & Record **120**:9-13 (July 2) 1924; **120**:60-62 (July 16) 1924.

21. Jones, C. M.: The Rational Use of Duodenal Drainage, Arch. Int. Med. **34**:60-78 (July 15) 1924.

these cases the crystals were clumped. One sixth of these gallbladder biles contained associated calcium crystals. Of the seventeen gallstones cases showing cholesterin crystals in the gallbladder bile at operation, in 35 per cent an appreciable number of these crystals (often clumped) were found in the duodenal bile before operation. This percentage would probably have been higher if the bile had been centrifugalized in every case. The presence of crystals in the duodenal bile does not, however, necessarily mean gallstones, since the former were found in the duodenal bile of 16 per cent of the gallbladder patients who presented no calculi at operation. However, where showers of crystals, including clumps, are found in the duodenal bile, gallstones will be found at operation in the majority of cases. In fact such clumps are miniature stones.

SUMMARY

This study is mainly based on a detailed analysis of the diagnostic findings in ninety-four consecutive operated patients with chronic gall tract disease.

Recent pathologic studies indicate that chronic gall tract disease involves not only a chronic cholecystitis but also a chronic interstitial hepatitis and a chronic cholangeitis with dilatation of the larger extrahepatic bile ducts. The relative degree of involvement of the gallbladder, bile ducts and liver varies greatly in the individual case, making it desirable to use various methods of diagnosis to obtain information regarding the involvement of these three parts of the biliary tree.

The history, when carefully taken, affords most valuable evidence for the presence of gall tract disease. Furthermore, it is indispensable to a correct functional diagnosis and a proper evaluation of the gastro-intestinal symptoms. This is especially important in patients who have evidence of several pathologic conditions in the gastro-intestinal tract.

The physical examination aids greatly in the differential diagnosis of gall tract disease from chronic irritable colon, chronic appendicitis, renal disease and other less common conditions.

Graham's contribution, cholecystography, affords reliable information about the gallbladder in a high percentage of cases, and has greatly refined gallbladder diagnosis. The oral administration of the dye is unobjectionable, and also reliable, if a proper and uniform technic is followed. In those cases presenting suggestive evidence of gallbladder disease in the cholecystograms, without definite clinical evidence, we prefer to repeat the oral method rather than resort to intravenous administration. Other roentgen-ray methods are still of value in a smaller percentage of cases, and should be used in conjunction with cholecystography.

Duodenobiliary drainage affords important direct evidence of chronic cholangeitis, and valuable indirect evidence of cholecystitis, in the finding of bile stained clumps of pus cells and bile stained colonies of bacteria, frequently in association with bile duct epithelium. Showers of clumped crystals in the bile strongly suggest gallstones.

By utilizing biliary drainage to determine the earliest stages of bile duct infection and inflammation, cholecystography to ascertain the pathologic physiology and anatomy of the gallbladder, and a serum bilirubin determination to gain some idea relative to the liver involvement, the diagnosis of early gall tract disease, suspected on the basis of clinical symptoms, can now be confirmed and refined.

As in other fields of diagnosis, a close correlation of the data obtained from various sources is of utmost importance.

THE RELATION OF MENSTRUATION TO THE PERMEABILITY OF THE SKIN CAPILLARIES AND THE AUTONOMIC TONUS OF THE SKIN VESSELS *

WILLIAM F. PETERSEN, M.D.
AND
GEORGE MILLES, S.B.
CHICAGO

In view of the intimate relation of the capillary permeability to autonomic and endocrine disturbances and the peculiar effect apparent in the reactivity of the skin, we have carried out a series of blister observations on a group of normal young women. The technic has been that described in the first article.[1]

That there is a change in capillary permeability preceding and during menstruation has been determined by Heilig and Hoff [2] and by Benda,[3] who have worked with dye injections and have found that the meninges becomes more permeable. Heilig and Hoff found in animal experimentation that thyroid extract and ovarian extract make the meninges more permeable.[4]

In the accompanying table we have tabulated the blister time and the permeability ratio in relation to the menstrual time. In the first part (*A*), menstrual and premenstrual observations show that in the premenstrual period the blister time is shortened (the skin is parasympathetic, the internal organs relatively sympathetic); with the onset of menstruation the skin becomes sympathetically oriented (the internal organs parasympathetic).

In the second part (*B*) the intermenstrual cases have been recorded, with a blister time that is a little longer than the menstrual and an average permeability ratio of 0.72, as compared to the premenstrual of 0.75 and the menstrual of 0.77.

These time relationships have been graphically shown in the accompanying chart.

---

* From the department of pathology, University of Illinois College of Medicine.

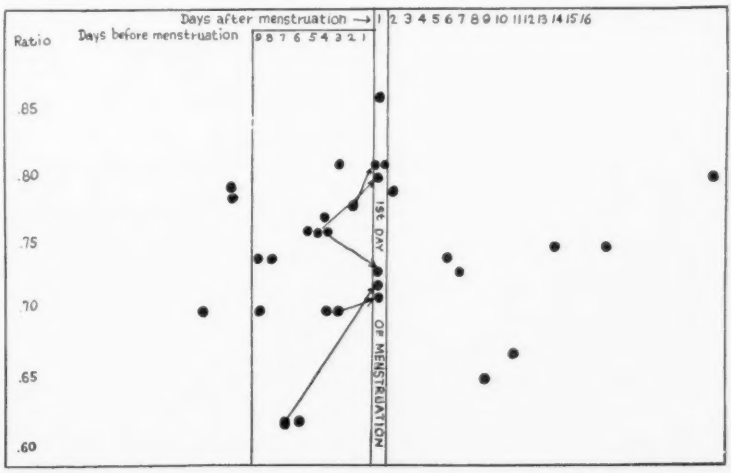
1. Petersen, W. F., and Willis, D. A.: Capillary Permeability and the "Inflammatory Index" of the Skin and in the Normal Person as Determined by the Blister, Arch. Int. Med. **38**:663 (Nov.) 1926.

2. Heilig, R., and Hoff, H.: Klin. Wchnschr. **3**:2049 (Nov. 4) 1924.

3. Benda, Robert: München. med. Wchnschr. **72**:1686 (Oct. 2) 1925.

4. Schrader (Mitt. a. d. Grenzgeb. d. Med. u. Chir. **34**:260, 1921) has approached the problem in another way. By means of local constriction he was able to determine that capillary hemorrhages took place readily in the skin in women from two to eight days before menstruation but ceased at once with the onset of menstruation.

	Time Relation to Menstruation	Blister Time: Before Menstruation Hours	Blister Time: During Menstruation Hours	Protein: In Serum, per Cent	Protein: In Blister, per Cent	Permeability Ratio: Before Menstruation	Permeability Ratio: During Menstruation	Blood Pressure: Systolic	Blood Pressure: Diastolic
	A								
	Menstrual and Premenstrual:								
6	Two days before	3	..	7.10	5.6	0.78	....	126	75
	Second day of menstruation...	..	5	8.04	6.566	....	0.81		
17	Three days before	8	..	7.416	5.294	0.71	....	122	75
	First day of menstruation.....	..	7½	7.73	5.41	....	0.70		
10	Four days before	1½	..	7.85	6.00	0.76	....	122	80
	First day of menstruation.....	..	6	8.064	5.9	....	0.73		
9	Five days before	3½	..	8.28	6.304	0.76	....	120	65
	First day of menstruation.....	..	5	8.064	6.5	....	0.80		
22	Seven days before	4	..	8.28	5.294	0.62	....	100	71
	First day of menstruation.....	..	4½	7.95	5.9	....	0.74		
	Menstrual:								
S81	First day of menstruation.....	..	5½	6.77	5.9	....	0.86		
4	Second day of menstruation...	..	5	7.416	5.9	....	0.79		
	Premenstrual:								
1	Five hours before onset of menstruation.....	3	..	8.28	6.708	0.81	....	108	80
2	Three days before	4	..	8.28	6.708	0.81	....	110	65
8	Four days before	3	..	7.85	6.00	0.77	....	110	70
18	Four days before	4	..	7.85	5.493	0.70	....	105	70
3	Five days before	3	..	8.28	6.64	0.80	....	130	60
7	Five days before	3½	..	7.85	6.102	0.76	....	138	80
	Average.....	3.6	5.5			0.75	0.77	117	72
	B								
	Intermenstrual:								
5	Eleven days before...		8	7.416	5.9		0.79	108	60
25	Eleven days before...		4½	7.73	6.160		0.79	118	68
11	Eighteen days after..		3	7.85	5.90		0.75	110	65
12	Fourteen days after.		5	7.20	5.40		0.75	112	68
13	Nine days before.....		2	7.95	5.90		0.74	112	80
14	Eight days before....		4	7.63	5.69		0.74	110	70
15	Six days after.....		3	7.85	5.82		0.74	90	60
16	Seven days after.....		8	7.632	5.6		0.73	102	75
24	Nine days before.....		3½	9.02	6.30		0.70	114	70
19	Thirteen days before		7½	8.06	5.695		0.70	108	68
20	Eleven days after....		6	8.40	5.695		0.67	128	68
21	Nine days after.....		4½	8.06	5.294		0.65	118	75
23	Nineteen days after..		7	7.85	4.89		0.62	98	70
	Average.....		5.8				0.72	110	69



Relation of permeability to period of menstruation: The black dots represent individual readings; when two determinations were made they were connected by a line.

Blood pressure examination has given the following results:

The average for the intermenstrual group was 110 systolic, 69 diastolic (thirteen examinations), while the premenstrual group averaged 117 systolic, 72 diastolic (eleven cases).

We were unable, in this relatively small group, to determine any relation of the permeability ratio to the incidence to influenza nor could we, in the absence of a complete examination, investigate the relation to tuberculous infection. It was of interest to note, however, that the young woman with the lowest ratio gave the most marked tuberculin reaction. In a general way, the intermenstrual cases all gave a more marked tuberculin reaction than the menstrual and premenstrual. The details will be published elsewhere.

COMMENT

In recent years a number of investigators have developed experimental evidence indicating that during the menstrual cycle an autonomic unbalance exists which begins approximately one week before the onset of menstruation and disappears in from three to six days after the beginning of menstruation.

Guillaume and Godel [5] contend that in menstruation we deal with an alternating preponderance of vagus and sympathetic tonus, the former beginning about a week before the onset and then alternating with a sympathetic tonus until about four days before the discharge.

Ludlum and McDonald [6] regard the phenomenon as wholly parasympathetic. They consider that a wave of vagus predominance begins from eight to two days before menstruation, at which time it reaches its maximum. Part of the effect, they believe, is due to the calcium in the blood after it has been liberated from the cells. That actual changes take place in the calcium has been demonstrated by Malamud,[7] who found that in 57 per cent of women examined during menstruation the calcium content of the serum was increased, in 14 per cent diminished.

Unfortunately no parallel potassium titrations were made. Callenberg [8] found the calcium level of the serum increased during menstrual urticaria and Andersen [9] finds the calcium content of the serum increased by approximately 1 mg. in the menstrual period.

It is obvious that many of the clinical observations of menstruation are indicative of an autonomic alteration. Moore and Cooper [10] inter-

5. Guillaume, A. C., and Godel, R.: Comp. rend. Soc. de biol. **90**:666 (March 21) 1924.
6. Ludlum, S. D., and McDonald, E.: Surg. Gynec. Obst. **41**:569 (Nov.) 1925.
7. Malamud, T.: Compt. rend. Soc. de biol. **91**:26 (June 13) 1924
8. Callenberg, J.: Klin. Wchnschr. **3**:533, 1924.
9. Andersen, W. T.: Hospitalstid. **68**:1177 (Dec.) 1925.
10. Moore, L. M., and Cooper, C. R.: Am. J. Physiol. **64**:416 (May) 1923.

pret the lowering of the pulse rate as parasympathetic in origin. The exaggerated motility and secretion of the stomach to which Hess and Faltitscheks [11] call attention is associated by them with the hyperirritability of the parasympathetic system, which they believe is due to an increased cholin production during menstruation.

We should like to call attention to one important source of confusion when the autonomic status of the organism is discussed, namely, the fact that the skin and periphery is under ordinary circumstances *oppositely* oriented from the splanchnic area.[12] Thus if the tonus of the skin shows an increase sympathetic, the splanchnic area will show an increase of the vagus tonus. To speak merely of a vagotonia during menstruation means relatively little unless we specify what general region of the body is under consideration.

We have been particularly interested in the determination of a possible change in capillary permeability during menstruation because of the direct influence of the menstrual cycle on a number of pathologic conditions.

It is daily gynecologic experience to find an activation of pelvic inflammation or the flare up of a pyelitis during menstruation; in medicine we may observe vicarious bleeding, an occasional icterus, migraine or even meningismus, as well as disturbances of the neurovascular apparatus; the dermatologist sees changes in skin reactivity; the rhinologist observes the menstrual rhinitis; the neurologist, the activation of a psychosis.[13]

Our own interest has centered chiefly on the effect in tuberculosis. From clinical experience it is known that the menstruating tuberculous woman shows evidence of focal activation as well as increased constitutional effects. Indeed, the effect on the temperature is so important that, having ruled out pelvic inflammation and pyelitis, a menstrual temperature increase is to be regarded as indicative of some relatively active tuberculous process. Kraus [14] has entered into a discussion of the phenomena and illustrates different types of reactions.

Here, then, we have a clear cut condition of biologic rearrangement whereby the organism becomes less resistant to the infection. Knowing these factors might lead us to an understanding of conditions that favor resistance to infection.

---

11. Hess, L., and Faltitschek, J.: Wien. Klin. Wchnschr. **38**:427 (April 16) 1925.

12. Müller, E. F., and Petersen, W. F.: Klin. Wchnschr. **5**:2, 1926.

13. Hoff (Deutsches Arch. f. klin. Med. **150**:1-2, 1926) has, for example, just published a series of latent cerebral conditions made manifest at the time of menstruation. He explains these on the basis of the increased permeability of the meninges, and on the increase in blood pressure in the premenstrual period.

14. Kraus, H.: Wien. med. Wchnschr. **4**:610, 1905.

We have demonstrated that at the onset of the premenstrual period the capillaries become more permeable and that changes take place in the autonomic innervation of the arterioles whereby the skin region becomes parasympathetic and the visceral area presumably sympathetic. There may be a slight increase of the metabolic rate at this time, although the evidence is conflicting (thyroid hyperfunction). If so, it will have no effect on the temperature of the normal woman because the skin can readily dissipate heat.

If, however, we have somewhere a tuberculous focus, the increase in permeability will have an effect quite comparable to a tuberculin injection, for the exchange of material to and from the focus is accelerated. Tuberculin is liberated from the tuberculous area. If the reaction at the focus is marked, local evidences of the activation may be obtained on physical examination.

The activation may become apparent in the premenstrual period by an increase in the temperature, or may appear as only a transient phenomenon as a temperature increase on the first day of menstruation. The first day or days seem to be particularly favorable for a rise in temperature because of the curious autonomic rearrangement whereby the skin tonus returns to the normal after having been vagotonic during the premenstrual time. The dissipation of heat would, therefore, be less rapid than before.

When we speak of the capillary permeability it should be kept in mind that the changes that we see in the capillary apparently apply to many of the other cellular elements, which probably become more permeable and are stimulated during the menstrual cycle. The increase in blood calcium must mean that tissue calcium is lessened, and presumably the tissue potassium will be found increased. These changes are not necessarily autonomic in the sense that we deal with changes induced by nerve impulses through the autonomic nervous system. They should be termed vegetative, and are induced by changes in ion equilibrium with coincident changes in the endocrine and autonomic nervous control. We would stress this point because much of the tissue that has to do directly with the resistance to the tubercle probably has no direct connection with the autonomic nervous system, or if so, in only a relatively negligible way. The change must take place through the more primitive ionic and hormonal routes.

Confusion exists because many of the agents that we commonly regard as autonomic stimulants *par excellance* really act directly on the cell membrane, irrespective of the nerve ending. Thus pituitary extract and epinephrine make cells less permeable in very high dilution, putting the cell actually into the rest phase, while the same agents may *stimulate*, through their effect on the autonomic ending, certain other cells, such as smooth musculature. Obviously, the specialized effect has been

superimposed on the more primitive and general protoplasmic effect, and yet it is the specialized effect that is commonly studied and regarded as of greatest importance.

Generally the agents that stimulate tissues (greater permeability) when acting directly on the cell membrane act parasympathetically—pilocarpine, thyroxin, cholin, muscarin, paraphenylendiamine—on the autonomic apparatus, while pituitary extract, epinephrine, calcium and insulin act in rendering the cell membrane less permeable when directly in contact with it, and sympathetically in reference to the autonomic nervous apparatus. But the autonomic nervous impulse in acting on the cell initiates a reaction (toward rest or toward activity) only in the direction that is determined by the ionic equilibrium of the membrane at the moment the impulse is received. A similar condition is probably true for the effect of the hormones, which must also use the ions as tools with which they may effect changes in cellular activity.

Menstruation represents a biologic rearrangement evidently involving an ionic change, an endocrine change, as well as an alteration in the autonomic nervous apparatus. The three forming the vegetative control of the tissues are the fundamental factors in the reaction of the organism to an infection. In menstruation the alteration, associated with an increased permeability of the capillaries and tissues, makes for less favorable conditions of resistance to tuberculosis. If we use the term vagotonia in the broad sense outlined above, we can term the menstrual cycle as one of vagotonia, and definitely associate this alteration as unfavorable for resistance to tuberculosis. We shall present other evidence supporting this view in further articles.

SUMMARY

Examination by means of the blister method has shown that the normal rate of permeability for skin capillaries is approximately 0.72 for the intermenstrual period, 0.75 for the premenstrual, and 0.77 for the menstrual period.

In the premenstrual period the skin tonus is parasympathetic; this seems to be promptly reversed with the onset of menstruation.

In the premenstrual and menstrual period the blood pressure average is higher than during the intermenstrual period.

The relation of these alterations to tuberculosis resistance is discussed.

HYPERTHYROIDISM, MYXEDEMA AND DIABETES*

RUSSELL M. WILDER, M.D.
ROCHESTER, MINN.

Many of the hypotheses concerning the rôle of the thyroid in carbohydrate metabolism have been based on observation of glycosuria in cases of hyperthyroidism and on the study of cases of frank diabetes, associated with diseases of the thyroid.

The literature contains a great number of references to evanescent glycosuria and hyperglycemia in patients with toxic goiter. These are common but by no means constant phenomena. After a test meal of 50 or 100 Gm. of glucose the blood sugar in such patients may rise to a higher level than is normal, and during the course of three or four hours a few grams of sugar, rarely more, may be excreted. At other times, even with restriction of the diet, there may be traces of sugar in the urine. The intravenous injection of glucose at uniform rates [1] has revealed that, whereas normal persons can be injected intravenously with glucose at a rate of 0.8 Gm. for each kilogram of body weight each hour without manifesting glycosuria, patients with hyperthyroidism may excrete sugar at injection rates of 0.6 or even 0.5 Gm. an hour for each kilogram. All such observations show that in hyperthyroidism the rate at which the body can assimilate glucose may be disturbed; they do not prove that anything is at fault with oxidation or reduction. Therefore, they do not indicate the existence of diabetes.

There is indeed good evidence to show that the utilization of carbohydrate is actually accelerated by hyperthyroidism in patients who do not have true diabetes. Following test meals of glucose in patients with exophthalmic goiter, as DuBois [2] and also Sanger and Hun [3] have shown, the respiratory quotients rise more abruptly than is normal. This observation has been repeatedly confirmed in this clinic. Whether it means rapid burning of carbohydrate or rapid reduction to fat may be debatable, but there can be no questioning the conclusion that it signifies a normal, or better than normal, utilization. In patients with frank

---

* From the Division of Medicine, Mayo Clinic.

* Read before the Association of American Physicians, Atlantic City, May 5, 1926.

1. Wilder, R. M., and Sansum, W. D.: d-Glucose Tolerance in Health and Disease, Arch. Int. Med. **19**:311-334 (Feb.) 1917.

2. DuBois, E. F.: Metabolism in Exophthalmic Goiter, Arch. Int. Med. **17**:915-964 (June) 1916.

3. Sanger, B. J., and Hun, E. G.: The Glucose Mobilization Rate in Hyperthyroidism, Arch. Int. Med. **30**:397-406 (Sept.) 1922.

diabetes the respiratory quotients are either sluggish or, if the diabetes is extreme, unchanged after the ingestion of sugar. It would seem, therefore, that while hyperthyroidism may, under certain conditions, alter the amount of sugar stored in the body, it can have no diabetogenic action. It is a looser use of the term "metabolism" to include under it such conceptions as absorption and storage, processes which do not involve oxidations or reductions of food materials. But only in this looser sense can there be said to be any proved alteration of carbohydrate metabolism in the great majority of patients with hyperthyroidism.

The literature contains far fewer frequent reports on cases of frank diabetes complicating hyperthyroidism, and the deductions regarding the significance of these rest as a rule on material that is too limited or too incompletely controlled to make them conclusive.

The present study is confined to the consideration of frank diabetes and is not concerned with transient or alimentary glycosuria. It involves an analysis of thirty-eight cases of persistent glycosuria (diabetes), fifteen in patients with exophthalmic goiter, twenty-three in patients with adenomatous goiter with hyperthyroidism, and one case of diabetes associated with myxedema. The differentiation of toxic goiter into adenomatous goiter with hyperthyroidism and exophthalmic goiter follows H. S. Plummer's classification.[4] In a preliminary report [5] based on a detailed study of the metabolism in four of these cases, the clinical importance of recognizing exophthalmic goiter in diabetes was emphasized and the following conclusions were drawn: The exophthalmic goiter syndrome reduces the ability of the diabetic patient to utilize carbohydrate; decreases the efficiency of the unit of insulin; increases the danger of sudden onset of diabetic coma, and the control of this syndrome by the administration of iodine markedly improves the carbohydrate tolerance. The evidence now submitted not only supports these conclusions but permits of their extension. In all of the cases here reported the diagnosis of hyperthyroidism has been confirmed by observation of the basal metabolic rate. In the operative cases, numbering thirty-two, the pathologic examination of the removed thyroid tissue is available. In fourteen of the patients with exophthalmic goiter the effect of the administration of iodine has been observed. The effectiveness of insulin in the presence of hyperthyroidism, the effect of thyroidectomy and other details, especially those bearing on treatment, have been considered.

4. Plummer, H. S.: Functions of the Normal and Abnormal Thyroid Gland, Oxford Medicine, New York, Oxford University Press, 1922, vol. 3, pp. 839-870.

5. Boothby, W. M., and Wilder, R. M.: Metabolism Studies in Exophthalmic Goiter Complicated by Diabetes, J. Clin. Investigation **1**:590, 1924-1925.

INCIDENCE

Fitz,[6] in an article from this clinic on the relation of hyperthyroidism to diabetes, sketched the older literature and himself reported thirty-nine cases of diabetes complicated by thyroid disease. In some of these he dealt only with nontoxic goiter, a condition that he found had no influence on the course of diabetes. I can confirm this conclusion. In a series of fifty-two cases of nontoxic adenomatous goiter there is no evidence that the course of diabetes or the effectiveness of insulin and dietetic management was altered, either by the presence of the goiter or as a result of its subsequent surgical removal. In the balance of Fitz' cases, twenty-two in number, the goiter was toxic. He had nine cases of diabetes among 1,800 cases of exophthamic goiter.

Table 1 indicates the frequency of occurrence of diabetes combined with states of hyperthyroidism as observed in the present series. The

TABLE 1.—*Incidence of Combined Diabetes and Hyperthyroidism* *

Disease	Cases	Complicating Disease	Cases	Per Cent of Total
Adenomatous goiter with hyperthyroidism	1,131	Diabetes	23	2.0
Exophthalmic goiter	2,340	Diabetes	15	0.6
Adenomatous goiter with hyperthyroidism and exophthalmic goiter, total	3,471	Diabetes	38	1.1
Diabetes	1,249	Adenomatous goiter with hyperthyroidism	23	1.8
		Exophthalmic goiter	15	1.1
		Adenomatous goiter with hyperthyroidism and exophthalmic goiter, total	38	3.0

* Mayo Clinic cases from Jan. 1, 1923, to Jan. 1, 1926.

number of combined cases is compared both to the number of cases of toxic goiter and to the number of cases of diabetes, observed during the period Jan. 1, 1923, to Jan. 1, 1926.

It appears from our clinical material that the incidence of frank diabetes as a complication of conditions of hyperthyroidism does not exceed 1.1 per cent. Its occurrence is more frequent in adenomatous goiter with hyperthyroidism (2 per cent) than in exophthalmic goiter (0.6 per cent). This is what should be expected from the fact that both diabetes and hyperthyroidism of adenomatous goiter are diseases for the most part of older people, whereas exophthalmic goiter occurs as a rule at an earlier age. In both groups the incidence of diabetes is certainly too small to justify the assumption that hyperthyroidism has much etiologic significance in diabetes. An etiologic relationship is

6. Fitz, Reginald: The Relation of Hyperthyroidism to Diabetes Mellitus, Arch. Int. Med. **27**:305-314 (March) 1921.

occasionally suggested by the simultaneous appearance of the two diseases, but in many instances in this series the date at which diabetes appeared can be established with reasonable certainty as preceding, often by several years, the first symptoms of hyperthyroidism.

THE RECOGNITION OF HYPERTHYROIDISM IN PATIENTS WITH DIABETES

The incidence of hyperthyroidism as a complication of diabetes may be somewhat greater than that shown in table 1. Seventeen cases were discarded because at the time of examination the basal metabolic rate was either normal or slightly elevated. Yet in many of these excluded cases there was good reason to believe that periods of hyperthyroidism had occurred previously. The recognition of mild grades of hyperthyroidism is often a difficult matter, and in the presence of diabetes it becomes doubly difficult owing to the fact that certain symptoms, notably bulimia, loss of weight and weakness, are common to both conditions. It should be remembered that the normal metabolism of well managed diabetic patients tends to be somewhat below the level called normal for fully nourished persons,[7] and that the greater the degree of subnutrition the greater will be the discrepancy. Consequently, a basal metabolic rate of + 10 or + 15, which would be considered as within the normal range for well nourished subjects, may represent in the case of an undernourished person with diabetes a definite stimulation from hyperthyroidism. We have come to recommend thyroidectomy when confronted with such conditions, particularly if the history suggests that periods of more intense hyperthyroidism have occurred previously.

In the presence of severe diabetic acidosis the symptoms of grave hyperthyroidism may be so masked as easily to escape detection. The following record of a case is illustrative:

REPORT OF CASE

CASE 1 (case 9, table 2).—A woman, aged 40, was admitted to the hospital, Oct. 21, 1924, in deep diabetic coma with carbon dioxide combining power 11 per cent by volume and blood sugar 0.4 per cent. Thyroidectomy had been performed in 1907 for exophthalmic goiter, but the general health had been good until recently. The patient had had two children in the interval and in 1921 had passed through a febrile condition thought to be encephalitis. Symptoms suggesting diabetes had developed abruptly in August, 1924. During the year prior to this the body weight had increased 50 pounds (22.7 Kg.). In the next two months it declined 30 pounds (13.6 Kg.).

The thyroid gland was barely palpable and no thrill or bruit was detectable. Ocular symptoms were not pronounced; however, a faint tremor, the warmth and sweatiness of the skin, and tachycardia suggested the possibility of recurrent exophthalmic goiter. Consequently compound solution of iodine was administered in addition to the more usual anticoma measures. The basal metabolic rate determined two days later was + 38.

7. Wilder, R. M.; Boothby, W. M., and Beeler, Carol: Metabolism of Diabetes, J. Biol. Chem. **51**:311-357 (April) 1922.

TABLE 2.—*Exophthalmic Goiter and Diabetes* *

Case	Age, Sex†	Disease	Duration, Months	Date	Height, Inches	Weight, Pounds: Normal	Weight, Pounds: Observed	Urine Sugar for 24 Hours, Gm.	Blood Sugar, per Cent	Compound Solution of Iodine for 24 Hours, Minims	Units of Insulin for 24 Hours	Glucose Equivalent of Diet, Gm.	Date	Basal Metabolic Rate	Remarks
1	45 ♀	Hyperthyroidism..... Diabetes.....	3 1	6/15/23	61	160	129	24	0.154	20	0	110	6/15/23	+56	
				6/25/23	..	...	...	1	0.105	20	0	110	6/25/23	...	Ligation
													7/ 7/23	+20	
				7/ 9/23	..	...	...	8	.....	20	0	100	7/ 9/23	....	Thyroidectomy
				1/16/24	..	...	133	0	0.160	0	0	Restricted	1/16/24	+13	
				4/ 6/26	..	...	140	0	.....	..	..	Restricted	1/28/24	+ 5	
2	69 ♀	.....	..	9/27/23	61	...	114	26	0.317	20	60	0	9/27/23	+72	Plasma carbon dioxide combining power, 10 per cent by volume
				10/29/23	..	...	...	92	0.276	0	50	95	10/29/23	+21	
				11/20/23	..	...	...	+	0.183	28	60	75	11/20/23	....	Thyroidectomy
				12/11/23	..	...	...	35	.....	20	50	85	12/11/23	+27	
				11/ 1/24	..	...	...	0	.....	0	35	90	11/ 1/24	....	Doing well
				4/ 8/26	..	...	...	±	.....	0	35	80			
3	19 ♀	Recurrent hyperthyroidism Diabetes.....	8 2	12/12/24	62	138	104	47	0.286	30	0	130	5/ 5/23	....	Thyroidectomy
				1/ 5/25	..	...	...	11	0.143	30	0	145	12/12/24	+59	
													1/ 5/25	+14	
				2/ 9/25	..	...	...	64	0.173	60	25	100	2/ 9/25	....	Thyroidectomy
				3/31/25	..	...	...	0	0.111	0	0	280	3/31/25	−27	
				4/ 8/26	..	...	116	0	.....	..	0	135			
4	20 ♂	Hyperthyroidism..... Diabetes.....	6 ? 3	8/ 7/24	75	195	145	57	0.192	0	20	70	8/ 9/24	+43	
				8/14/24	..	...	...	35	0.225	90	90	100	8/19/24	− 2	
				8/19/24	..	...	...	0	0.100	30	90	140			
				9/12/24	..	...	...	Trace	.....	30	50	140	9/12/24	+ 1	
				9/14/24	..	...	...	5	.....	30	60	140	9/13/24	....	Thyroidectomy
				9/26/24	..	...	...	0	.....	20	20	100	9/26/24	− 4	
				6/11/25	..	...	...	11	0.157	0	30	100	6/11/25	− 5	
5	43 ♀	Hyperthyroidism..... Diabetes.....	6 1	1/ 7/25	61	152	130	51	0.210	0	0	120	1/ 5/25	+50	Chart 1
				1/23/25	..	...	...	9	0.182	30	20	130	1/24/25	+25	
				1/26/25	..	...	...	37	.....	40	30	55	1/26/25	....	Thyroidectomy
				2/11/25	..	...	...	0	0.133	20	0	150	2/11/25	+ 5	
				12/ 9/25	..	...	...	0	0.113	0	0	250	12/10/25	+ 5	
				4/ 6/26	..	...	129	0	.....	..	0	130			
6	20 ♂	Hyperthyroidism..... Diabetes.....	8 8	2/ 3/24	69	160	114	49	0.375	15	50	70	2/ 5/24	+38	
				2/11/24	..	...	...	0	0.110	15	30	75	2/15/24	0	
													2/22/24	....	Thyroidectomy
				3/ 5/24	..	...	...	0	.....	0	10	130	3/ 5/24	....	Left without dismissal; untrained in dieteties
													9/15/24	....	Reported dead from diabetes

7	63 ♀	Diabetes..... Hyperthyroidism.....	4+ 2	9/ 5/25	62	180	125	+	0.350	0	0	Not restricted	9/ 4/25	+42	
				9/14/25	..	...	...	29	.....	0	0	140	9/16/25	+40	
				10/ 8/25	..	...	...	0	.....	30	40	140	10/ 8/25	+36	
				10/14/25	..	...	...	17	.....	0	40	100	10/12/25	+39	
				10/22/25	..	...	...	0	.....	0	0	140	10/13/25	....	Thyroidectomy
				4/ 9/26	..	...	...	+					4/ 9/26	...	Not well trained in dietetics
8	44 ♀	Diabetes..... Hyperthyoridism.....	? 12	7/23/25	64	...	217	48	0.312	30	0	Not restricted	7/18/25	+45	
													7/23/25	+28	
				8/ 2/25	..	...	...	Trace	.....	30	0	155	8/ 1/25	+26	
				8/ 9/25	..	...	...	15	.....	30	55	155	8/ 7/25	....	Thyroidectomy
				8/15/25	..	...	...	0	.....	30	0	240			
				8/18/25	..	...	...	..	0.230						
				4/ 6/26	..	...	230	0					4/ 6/23	....	Not following diet
9	40 ♀	Recurrent hyperthyroidism	3	10/21/24	63	188	146	11	0.400	0	110	100	11/ 5/07	....	Thyroidectomy
													10/21/24	....	Plasma carbon dioxide combining power, 11 per cent by volume
		Diabetes.....	2												
				10/23/24	..	...	...	24	.....	40	50	100	10/23/24	+38	No acidosis
				11/12/24	..	...	...	0	0.255	20	60	100	11/12/24	+12	
				3/19/25	..	...	...	38+	.....	..	60	80	3/19/25	....	Plasma carbon dioxide combining power 10 per cent by volume; tincture of iodine painted on skin
				3/25/25	..	...	...	27	0.241	30	80	100	3/25/25	+47	
				3/31/25	..	...	...	0	0.241	45	90	140	3/31/25	+20	Compound solution of iodine discontinued
				4/14/25	..	...	...	15	.....	0	90	140	4/14/25	+48	Compound solution of iodine resumed
				5/12/25	..	...	...	0	.....	40	40	140	5/12/25	+12	
				1/ 2/26	..	...	...	+	0.358	90	60	100	1/ 2/26	....	Plasma carbon dioxide combining power, 21 per cent by volume
				1/11/26	..	...	...	14	0.261	60	75	140	1/ 5/26	+45	
				1/13/26	..	...	...	21	.....	60	80	100	1/12/26	....	Thyroidectomy
				3/18/26	..	...	140	0	0.200	30	40	140	3/18/26	−16	
10	57 ♀	Diabetes..... Hyperthyroidism.....	2+ 2	7/ 9/25	61	157	112	54	0.154	30	0	Not restricted	7/ 2/25	+61	
													7/10/25	+27	
				7/16/25	..	...	...	Trace	0.154	30	0	180	7/16/25	+12	
				7/31/25	..	...	...	71	.....	80	0	40	7/30/25	....	Thyroidectomy
				8/ 1/25	..	...	...	24	.....	80	65	50	8/ 1/25	....	Acetonuria
				8/10/25	..	...	...	0	0.110	30	0	140			
				4/16/26	..	...	129	0					4/16/26	....	Diet restricted

* The records of the cases in tables 3 and 4 have been sharply abbreviated. The duration of hyperthyroidism is judged from the time of appearance of tachycardia, heat intolerance and nervousness; that of diabetes from the time of appearance of polyuria, polydipsia and glycosuria. The term "glucose equivalent" originated with Woodyatt. Its use implies the assumption that 100 per cent of the carbohydrates, 58 per cent of the proteins and 10 per cent of the fats of the diet pass through the stage of glucose during the processes of assimilation. In none of the diets did the proteins exceed 70 Gm. All blood sugar determinations were made with the Folin-Wu technic on venous blood drawn in the morning before the patient had had breakfast. The insulin used was supplied by the Eli Lilly Company, and the units of insulin referred to are the clinical units standard in the United States and Canada.

† In this and table 4 ♂ indicates male, ♀ female.

TABLE 2.—*Exophthalmic Goiter and Diabetes.—Continued*

Case	Age, Sex	Disease	Duration, Months	Date	Height, Inches	Weight, Pounds: Normal	Weight, Pounds: Observed	Urine Sugar for 24 Hours, Gm.	Blood Sugar, per Cent	Compound Solution of Iodine for 24 Hours, Minims	Units of Insulin for 24 Hours	Glucose Equivalent of Diet, Gm.	Date	Basal Metabolic Rate	Remarks
11	42 ♀	Hyperthyroidism..... Diabetes.....	2 2	12/16/22	69	200	154	Trace	0.227	0	0	100	12/ 8/22	....	Urine contained much sugar and acetone on admission
				.....	..	...	...	..					12/19/22	+67	
				1/ 9/23	..	...	...	0	0.160	10	0	120	1/ 9/23	+35	
				2/ 2/23	..	...	...	0	.....	0	0	100	1/15/23	....	Thyroidectomy
				12/ 4/23	..	...	...	13	0.250	0	0	Restricted	12/ 7/23	— 6	
				5/22/24	..	...	...	24	0.275	0	0	100	5/28/24	0	Diabetes more severe
				4/ 6/26	..	...	156	0	.....	..	35	105			

Cases Without Operation

Case	Age, Sex	Disease	Duration, Months	Height, Inches	Weight, Pounds: Normal	Weight, Pounds: Observed	Remarks
12	49 ♀	Hyperthyroidism..... Diabetes.....	28 6	?	152	110 ?	The presence of exophthalmic goiter, although strongly suggested by the patient's history and symptoms, was unrecognized by several physicians at previous examinations. Admitted to hospital Jan. 29, 1923, with diabetic acidosis. The seriousness of the case did not impress house officers until the laboratory reports, January 30, showed plasma carbon dioxide combining power 18 per cent by volume and blood sugar 0.420 per cent. The usual anticoma measures were then instituted, but the patient died two hours later. The pathologist reported a small hypertrophic parenchymatous thyroid, typical of exophthalmic goiter
13	41 ♀	Diabetes..... Hyperthyroidism.....	60 12 ?	62	125	101	This patient was observed in the hospital in April and May, 1925. The basal metabolic rates during the first week ranged from +17 to +24. The thyroid was small and lumpy; there was no bruit, but a definite tremor and high pulse rate suggested hyperthyroidism. Compound solution of iodine was given, and the basal metabolic rate fell to +1, accompanied by improved tolerance. The patient was dismissed on a diet with a glucose equivalent of 100 Gm., taking 30 units of insulin. No reply was received to an inquiry dated April 1, 1926
14	45 ♂	Hyperthyroidism..... Diabetes.....	18 12	69	?	150	Hospital observation from Feb. 20 to March 9, 1925: a small diffuse enlargement of the thyroid, tachycardia on slight exertion, quadriceps weakness, a slight stare, and loss of weight disproportionate to the mild diabetes, led to the suspicion of exophthalmic goiter. Blood sugar was 0.2 per cent. The basal metabolic rates after a week in the hospital were +21 and +17. The use of compound solution of iodine caused these to fall and promptly checked the glycosuria, the diet being held the same, with a glucose equivalent of 140 Gm. Thyroidectomy was advised but refused, and the patient left with intentions of continuing the same diet and the use of iodine. A letter received Oct. 22, 1925, stated "health was poor"; report received April 6, 1926, said: taking compound solution of iodine, diet with glucose equivalent of 145 Gm. and no insulin; urine sugar was 0 and weight 155 pounds
15	42 ♀	Hyperthyroidism..... Diabetes.....	168 11	62	135	110	Hospital observation from Feb. 21 to March 21, 1923: blood sugar on admission was 0.285 per cent and basal metabolic rate +15; tolerance with 25 units of insulin for diet with glucose equivalent of 155 Gm.; history of exophthalmic goiter with first symptoms in 1909; thyroidectomy was performed elsewhere in 1911; symptoms recurred and a second thyroidectomy was performed in 1914; periodic recurrence of symptoms later; diabetic symptoms first noted in January, 1922; never very severe. This patient was a very intelligent woman and very conscientious about her diet; nevertheless she died at home in diabetic coma, Nov. 3, 1923

This patient was readmitted, March 19, 1925, again with severe acidosis, the carbon dioxide combining power of the plasma being 10 per cent by volume. She had followed instructions regarding diet and insulin fully, but on her own initiative had discontinued the taking of iodine a few days prior to this attack of acidosis. There was no history of any infection or other cause for her acidosis. In treatment, iodine was again resorted to. This time it was painted on the skin in the form of a tincture as compound solution of iodine was not retained when given by mouth or by enema because of persistent vomiting and the irritability of the rectum. After twenty-four hours, vomiting ceased and compound solution of iodine was administered by mouth. The basal metabolic rate was not determined until March 25. It was then + 47.

In order to observe the effect of discontinuing iodine none was given after March 31, by which time the basal metabolic rate had decreased to + 20. The diet was held constant at 2,100 calories and a glucose equivalent[8] of 140 Gm. The insulin dosage was 90 units, and on this regimen the urine was free from sugar and acetone. The basal metabolic rate climbed gradually and reached + 48, April 14; simultaneously sugar reappeared in the urine and increased in amount from day to day. The condition of the patient and the nervousness, tremor and tachycardia became distinctly worse. Acetone appeared and the carbon dioxide combining power of the plasma fell again to 30 per cent by volume. The use of compound solution of iodine was therefore resumed. By May 12 the basal metabolic rate was lower and with the same diet the insulin requirement had fallen to 40 units.

Jan. 2, 1926, this patient was again admitted in a state of serious acidosis. Again she had been careless about iodine and discontinuing it had been followed by epigastric pain, vomiting and hyperpnea. The first basal metabolic rate was obtained January 5; it was then + 45. Thyroidectomy was performed January 12. The weight of the tissue removed was 22 Gm. It showed hypertrophic parenchyma with areas of thyroiditis. The subsequent course was uneventful. At the last examination, April 18, 1926, the basal metabolic rate was — 16, the diet had a glucose equivalent of 140 Gm. and the insulin requirement was 40 units.

This case illustrates a number of topics that will receive consideration. It is cited here particularly to emphasize how readily exophthalmic goiter may escape detection when it is complicated by the alarming symptoms of diabetic acidosis. In cases 2 and 4 (table 2) the patient was likewise in a serious state of diabetic acidosis when first seen. In neither of them was hyperthyroidism very evident, yet both patients improved rapidly after compound solution of iodine was given and might well have died had it been withheld. In the fatal case (case 12, table 2), also included in a recent report of necropsy findings in cases of diabetes,[9] the patient was admitted in diabetic coma; exophthalmic goiter was not suspected until the pathologist found hypertrophic parenchymatous tissue in the thyroid. The possibility of hyperthyroidism should therefore be borne in mind in every case of diabetic acidosis and if suggestive symptoms, particularly tremor and marked tachycardia, are present, Lugol's solution should be given.

---

8. The glucose equivalent of a diet is calculated according to R. T. Woodyatt's suggestion (Objects and Method of Diet Adjustment in Diabetes, Arch. Int. Med. **28**:125-141 [Aug.] 1921), by the formula $G = C + 0.58\ P + 0.1\ F$, in which G is glucose equivalent, C carbohydrate, P protein, and F fat.

9. Wilder, R. M.: Necropsy Findings in Diabetes, South. M. J. **19**:241-248, 1926.

Holst,[10] from recent experience, advises examination for hyperthyroidism in all cases of diabetes. The urgent necessity for this and for thorough control of hyperthyroidism in cases of diabetes is illustrated by case 15 (table 2). This patient was an intelligent woman, a visiting nurse, well trained in the management of diabetes and very conscientious. Yet she died at her home in coma without having altered her regimen and without having acquired any infection or other cause than hyperthyroidism for this sudden exacerbation of her diabetes. She had had exophthalmic goiter and the gland was partially resected in 1911. Recurrence of symptoms required a second operation in 1914. Diabetes, acute in onset, started in January, 1922. In March, 1922, the basal metabolic rate was + 17. In February, 1923, it was + 15. As she was markedly undernourished these rates were probably significant.

THE EFFECT OF HYPERTHYROIDISM ON DIABETES

Contrary to the view first proposed, I think, by Friederich Müller,[11] there is little justification for the assumption that hyperthyroidism can initiate diabetes in an otherwise unpredisposed person. The small incidence of the combined diseases argues too strongly against it. Nor are there adequate grounds for the belief of Holst,[12] Falta [13] and others that a special type of diabetes may be provoked by hyperthyroidism. On the other hand, there is no doubting the evidence that frank diabetes once existent is seriously aggravated by hyperthyroidism, or that a mild and possibly inconspicuous or latent spark of diabetes may be fanned into flame by hyperthyroidism.

Thyroid extract fed to normal persons will occasionally, but by no means always, provoke an alimentary type of glycosuria similar to that observed in some patients with hyperthyroidism. Such glycosuria so seldom develops into frank diabetes that when it does, as in the cases cited by Friederich Müller, it is probable that true diabetes preexisted. On the other hand, when thyroid is given to patients with diabetes, a marked intensification of glycosuria occurs and persists some time after the drug is discontinued. Grawitz [14] reported such an experiment in 1897. In table 3 are the abbreviated laboratory data obtained in a case of mild diabetes in which desiccated thyroid was fed. The disease in

10. Holst, Johan: Glycosuria and Diabetes in Exophthalmic Goiter, Acta med. Scandinav. **55**:302 (June) 1921.

11. Müller, F.: Discussion of paper by Kraus, F.: Verhandl. d. Cong. f. inn. Med. **23**:100, 1906.

12. Holst, Johan: Kohlenhydratstoffwechselanomalien und Pankreasveränderungen bei Morbus Basedowii, Schweiz. med. Wchnschr. **53**:725-729 (Aug. 2) 1923.

13. Falta, W.: Endocrine Diseases, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1923, p. 88.

14. Grawitz, E.: Morbus Basedowii compliziert mit Diabetes Mellitus nebst Bemerkungen über Iodthyrinwirkung, Fortschr. de Med. **15**:849-853, 1897.

this case was under good control by diet without the use of insulin. The diet was held constant and for a period of nine days, beginning April 25, a total of 42 grains (3 Gm.) of desiccated thyroid was administered. This produced an elevation of the basal metabolic rate from an average level of —7 to a maximal of + 20, and coincidently sugar appeared in the urine in amounts exceeding that which could possibly be accounted for by the accompanying accelerated catabolism of protein. When the drug was discontinued glycosuria persisted to such an extent that a restricted dietary and insulin were necessary to control it. Later, after the basal metabolism had again fallen to normal, the previous good tolerance returned.

TABLE 3.—*Effect of Thyroid on Tolerance in a Case of Mild Diabetes* *

Date, 1925	Desiccated Thyroid, Grains	Basal Metabolic Rate	Blood Sugar, per Cent	Urine	
				Sugar, Gm.	Nitrogen, Gm.†
4/22	...	....	0.100	0	8
4/23	...	— 7	0.112	0	7
4/24	...	— 7	0.102	0	10
4/25	3	—12	0.118	0	7
4/26	9	....	....	..	..
4/27	9	— 8	0.143	5	14
4/28	3	+15	0.156	12	7
4/29	3	+16	0.171	15	10
4/30	3	+ 8	0.144	..	..
5/ 1	5	+14	0.156	20	9
5/ 2	6	+15	0.185	37	20
5/ 3	2	+19	.....	..	..
5/ 4	...	+20	0.153	24	12
5/ 5	...	....	0.154	42	18
5/ 6	...	+19	0.154	24	14
5/17	...	....	.....	0	7
5/18	...	....	.....	0	8
5/19	...	— 3	0.118	0	7

* The diet consisted of carbohydrates, 98 Gm.; proteins, 48 Gm., and fats, 242 Gm.; glucose equivalent, 150 Gm.
† Twenty-four hours.

A number of cases could be cited to illustrate the fact that preexisting diabetes is markedly intensified by the occurrence of hyperthyroidism. The date of onset in hyperthyroidism is often difficult to determine. The same is true in diabetes. In the following case, however, it is reasonably certain that diabetes had existed for at least two years while hyperthyroidism was not older than six months.

CASE 2 (case 4, table 4).—A woman, aged 59, developed marked polyuria and polydipsia in February, 1922. Sugar was found in the urine, but this was readily controlled by a diet until, in Augst, 1924, symptoms suggestive of hyperthyroidism were noted for the first time. These were nervousness, intolerance to heat, increased perspiration and tachycardia. Thereafter, dieting proved ineffectual, and at the time of admission to the hospital, Feb. 16, 1924, the urine contained an abundance of sugar and the blood 0.252 Gm. of sugar for each 100 cc. On a diet with a glucose equivalent of 140 Gm. an average of 50 Gm. of sugar appeared in the urine daily. The basal metabolic rates ranged from + 52 to + 66. Later, glycosuria was controlled with insulin, 40 units daily, and, March 5, thyroidectomy was performed. Thyroid tissue weighing 372 Gm. was removed; this showed multiple adenomas. The convalescence was uneventful; the basal metabolic rate fell, and by March 26 the same diet, previously requiring 40 units of insulin, could be taken without insulin.

TABLE 4.—*Adenomatous Goiter with Hyperthyroidism and Diabetes*

Case	Age, Sex	Disease	Duration, Months	Date	Height, Inches	Weight, Pounds: Normal	Weight, Pounds: Observed	Urine Sugar for 24 Hours, Gm.	Blood Sugar, per Cent	Compound Solution of Iodine for 24 Hours, Minims	Units of Insulin for 24 Hours	Glucose Equivalent of Diet, Gm.	Date	Basal Metabolic Rate	Remarks
1	66	Diabetes	6	9/21/25	62	170	126	Trace	0.211	0	0	Restricted	9/22/25	+43	
	♀	Hyperthyroidism	3	9/29/25	..	...	...	22	.....	0	0	170	9/29/25	+37	
				10/ 8/25	..	...	...	Trace	.....	20	50	70	10/ 7/25	....	Thyroidectomy
				10/29/25	..	...	...	0	.....	0	0	170			
				4/ 7/26	..	...	146	Trace	.....	..	0	135			
2	58	Diabetes	36	6/12/25	61	150	98	11	0.230	0	0	90	05	....	Thyroidectomy
	♀	Recurrent hyperthyroidism		6/15/25	..	...	...	14	.....	0	50	200	6/10/25	+29	
				6/20/25	..	...	...	12	0.176	0	25	100	6/17/25	....	Thyroidectomy
				7/ 3/25	..	...	...	0	0.126	0	25	100			
				4/ 8/26	..	...	112	0	.....	..	35	Restricted			
3	54	Hyperthyroidism	12	4/ 9/23	62	170	136	4	0.182	10	25	80	4/ 9/23	+51	
	♀	Diabetes	6	4/13/23	..	...	...	15	.....	10	25	145	4/13/23	+41	
				4/17/23	..	...	...	67	.....	10	10	75	4/16/23	....	Thyroidectomy
				4/28/23	..	...	...	0	.....	0	15	100	4/28/23	+15	
				4/ 6/26	..	...	165	Trace	.....	..	15	115			
4	59	Diabetes	24	2/18/24	64	206	124	64	0.252	0	0	140	2/18/24	+66	
	♀	Hyperthyroidism	6	3/ 7/24	..	...	...	20	0.235	0	20	100	3/ 5/24	....	Thyroidectomy
				3/26/24	..	...	...	0	.....	0	0	150	3/26/24	+ 9	
				7/17/24	..	...	. .	0					7/17/24	....	Well
				10/ 7/24	..	...	...	..					10/ 7/24	....	Died; acute cholecystitis ?
5	51	Hyperthyroidism	36	12/ 6/24	61	160	150	11	0.227	0	0	150	12/ 3/24	+42	
	♀	Diabetes	30	12/15/24	..	...	...	0	0.200	30	35	150	12/ 6/24	+21	
				12/18/24	..	...	...	40	0.286	30	70	50	12/16/24	....	Thyroidectomy
				1/30/25	..	...	...	0	0.133	20	0	70			
				1/ 2/26	..	...	...	0	.....	..	0	Restricted			
6	53	Diabetes	84	7/ 1/24	63	170	101	84	0.227	0	0	140	7/ 2/24	+36	
	♀	Hyperthyroidism	6	7/ 9/24	..	...	...	0	0.200	0	90	140			
				7/15/24	..	...	...	55	0.250	0	90	100	7/14/24	....	Thyroidectomy
				7/29/24	..	...	...	0	.....	0	0	100	7/30/24	+12	
				8/18/25	..	...	...	+	.....	..	0	Increased			
7	49	Hyperthyroidism	12	7/ 6/25	63	245	180	14	0.206	20	30	150	7/ 6/25	+30	
	♀	Diabetes	4	7/19/25	..	...	...	10	.....	30	40	150	7/17/25	....	Thyroidectomy
				8/ 4/25	..	...	...	0	0.117	0	0	140	8/ 3/25	+ 8	
				4/ 7/26	..	...	200	+	.....	..	0	135			
8	56	Hyperthyroidism	12	1/10/24	59	145	123	115	0.270	0	0	Unrestricted	1/15/24	+37	
	♀	Diabetes	12	1/22/24	..	...	...	Trace	0.157	0	20	60	1/22/24	+23	
				1/29/24	..	...	...	50	.....	0	40	100	1/28/24	....	Thyroidectomy
				2/15/24	..	...	...	0	.....	0	15	120			
				4/15/26	..	...	135	Trace	.....	..	0	Not restricted			

9	44 ♀	Diabetes..... Hyperthyroidism.....	60 48	12/11/24 12/26/24 1/ 5/25 4/ 7/26	64	153	110 22 0 0	Trace 0.115	0.176 45 0 ..	0 0 0 0	100 100 100 95	12/13/24 12/24/24 1/ 5/25	+18 .... −12	Thyroidectomy
10	62 ♂	Diabetes..... Hyperthyroidism.....	240 6	10/27/24 11/ 5/24 11/ 7/24 12/ 4/24 1/11/26 4/ 8/26	67	210	159 61 5 97 0 0 0	0.200 .... 0.120	0 30 30 0 0 ..	0 65 80 0 0 0	140 140 100 100 100 145	10/27/24 11/ 4/24 11/ 6/24 1/11/26	+40 +30	Thyroidectomy Subsequent admission
11	45 ♂	Diabetes..... Hyperthyroidism.....	108 18	8/21/25 8/25/25 9/14/25 4/ 6/26	68	210	163 25 0 0	Trace 0.095	0.171 0 0 ..	0 30 0 ..	90 100 140 135	8/21/25 8/24/25	+30	Thyroidectomy
12	63 ♀	Diabetes..... Hyperthyroidism.....	72 ?	6/30/25 9/13/25 9/24/25 4/ 6/26	66	220	189 Trace Trace 0 0	0.155 ..... 0.154	0 30 0 ..	0 30 0 0	140 100 140 Restricted	6/29/25 9/11/25	+32	Thyroidectomy
13	56 ♂	Diabetes..... Hyperthyroidism.....	120 4	10/28/24 11/15/24 11/26/24	68	180	140 13 4 0	0.182 0.213 0.143	0 40 30	0 20 0	Not restricted 100 150	10/28/24 11/14/24 11/26/24 6/ 9/25	+39	Thyroidectomy Heart weak; coronary sclerosis Sudden death due to heart
14	46 ♀	Diabetes..... Hyperthyroidism.....	60 48	10/12/24 11/ 3/24 11/ 5/24 11/14/24 10/26/25	56	180	164 50 Trace + 0 +	0.250 0.194 0.235 0.110	0 0 0 0 ..	0 30 30 0 0	Restricted 140 100 140 Not restricted	10/21/24 10/28/24 11/ 4/24 11/11/24	+20 +11 .... + 7	Thyroidectomy
15	62	Hyperthyroidism..... Diabetes.....	12 ? 8	2/20/24 5/23/24 4/ 7/26	60	165	121 0 0 153	0.120 0.158	0 0 ..	0 0 ..	Restricted 140 Restricted	2/20/24 5/24/24	+23	Thyroidectomy
16	62 ♀	Hyperthyroidism..... Diabetes.....	? 9	4/25/25 5/10/25 4/ 6/26	64	225	191 10 170	Trace 0.201	0.162 0 ..	0 20 0	52 100 95	4/28/25 5/ 8/25	+30	Thyroidectomy
17	52 ♀	Diabetes..... Hyperthyroidism.....	17 12	7/18/23 8/ 1/23 8/ 7/23 4/15/26	61	170	130 44 0 ?	Trace	0.190 0 0 ..	0 40 0 0	Restricted 160 160 Restricted	7/18/23 7/31/23	+18	Thyroidectomy
18	65 ♂	Hyperthyroidism..... Diabetes.....	48 48	10/18/23 11/ 7/23 11/12/23	68	195	128 17 19 0	....	0 10 0	0 20 0	200 100 140	10/19/23 11/ 6/23	+16	Thyroidectomy
19	56 ♀	Hyperthyroidism..... Diabetes.....	24 24	8/ 2/23 8/ 9/23	64 ..	175 ...	138 5 7	0.200 0.246	0 0	0 0	140 140	7/30/23 7/31/23 8/ 6/23 9/ 3/23 12/26/24	+42 +25	Thyroidectomy Amputation of breast for carcinoma Died; recurrent carcinoma

TABLE 4.—*Adenomatous Goiter with Hyperthyroidism and Diabetes—Continued*

Case	Age, Sex	Disease	Duration, Months	Date	Height, Inches	Weight, Pounds: Normal	Weight, Pounds: Observed	Urine Sugar for 24 Hours, Gm.	Blood Sugar, per Cent	Compound Solution of Iodine for 24 Hours, Minims	Units of Insulin for 24 Hours	Glucose Equivalent of Diet, Gm.	Date	Basal Metabolic Rate	Remarks
20	45 ♀	Hyperthyroidism..... Diabetes.....	? 14	8/21/23	64	148	128	14	0.197	0	0	130	8/17/23	+23	
													8/23/23	+23	
				8/27/23	..	...	...	45	.....	0	20	130	8/24/23	....	Thyroidectomy
				8/30/23	..	...	...	70	0.259	..	20	130			
				9/ 8/23	..	...	...	0	.....	0	20	130			
				9/14/23	..	...	...	0	.....	0	0	130	9/15/23	+16	
				4/ 6/26	..	...	145	Trace	.....	..	0	80			
21*	65 ♂	Diabetes..... Recent hyperthyroidism	36 ? ..	4/13/23	69	180	152	11	0.240	0	0	Not restricted	4/14/23	+18	
				4/27/23	..	...	...	45	0.263	..	..	Restricted	4/23/23	...	Thyroidectomy
				5/21/23	..	...	...	5	.....	..	..	Restricted			
				5/28/23	..	...	...	29	0.325	..	60	100	5/22/23	....	Suprapubic cystostomy for carcinoma
													5/30/23	....	Death from acidosis, pneumonia and uremia

Cases Without Operation

				Height, Inches	Weight, Pounds: Normal	Weight, Pounds: Observed	
22	72 ♀	Hyperthyroidism..... Diabetes.....	31 31	61	?	95	Hospital observation from Oct. 17 to Nov. 11, 1923: a small adenomatous thyroid, marked arteriosclerosis and dilatation of the heart were noted; on admission, despite a previously restricted diet, the urine contained sugar and the blood sugar was high, 0.305 per cent; although the diet was further restricted to a glucose equivalent of 40 Gm., the glycosuria and hyperglycemia persisted and could only be controlled by relatively large doses of insulin. The basal metabolic rates were +20 and +14. A second hospital observation was made Dec. 20, 1923, at which time the patient was bedridden because of increased weakness and cardiac decompensation; basal metabolic rate +20; compound solution of iodine was given and a later basal metabolic rate was +9; the patient steadily declined; was discharged and died at her home Feb. 19, 1924; necropsy was not performed
23	63 ♀	Diabetes..... Hyperthyroidism.....	180 ?	61	137	125	Hospital observation from July 10 to Aug. 16, 1924: basal metabolic rates, +25, +22 and +21; 30 units of insulin required with diet with glucose equivalent of 90 Gm.; the fasting blood sugar, August 7, was 0.191 per cent; thyroidectomy not advised because of evidence of complicating angina pectoris; report, April 6, 1926, was weight, 136 pounds; urine sugar, 0; 10 units of insulin daily and diet restricted

* After the prostatic operation this patient developed an acute exacerbation of his mild diabetes, possibly the result of infection in the wound from thyroidectomy; old abscess seen at necropsy.

In this patient a mild diabetes was made fairly severe by the development of hyperthyroidism, and resumed its mild state after the control of the latter by thyroidectomy.

Hyperthyroidism, as is well known, is wont to show alternating periods of exacerbation and remission. This is true both in that accompanying adenomatous goiter and in exophthalmic goiter, although it is much more common in exophthalmic goiter. Exacerbations may occur spontaneously and these at times assume the intense form of the hyperthyroid crisis. When diabetes coexists, any exacerbation is associated with intensified glycosuria and this may be so extreme that not enough sugar is burned to prevent ketosis. Under such circumstances acetone formation goes on apace, and serious acidosis and coma may result. In case 1 (case 9, table 2) already cited in detail, there is good reason to believe that the three attacks of diabetic acidosis, the first two actual diabetic coma, were precipitated in this manner. The same is probably true of cases 2 and 4 of table 2.

It is furthermore a frequent occurrence to have an exacerbation of hyperthyroidism within from six to twenty-four hours after thyroidectomy, and in patients with complicating diabetes one almost always sees an exacerbation of the diabetic condition on the day following operation. Large doses of insulin, from 80 to 100 units daily, may be necessary for its control (tables 3 and 4).

THE INFLUENCE OF IODINE ON THE INTENSITY OF DIABETES

In cases of diabetes uncomplicated by hyperthyroidism iodine is without observable effect. At the Mayo Clinic, I have administered it periodically to a large group of patients with diabetes and have been unable to detect any change in tolerance attributable to it. In cases of diabetes with adenomatous goiter and hyperthyroidism it has likewise been ineffectual except in a few instances in which the diagnosis of coexisting exophthalmic goiter could not be excluded. In cases of diabetes complicated by frank exophthalmic goiter the influence of iodine on the intensity of the diabetic process is as striking as its effect on the exophthalmic goiter syndrome. Labbé [15] noted this in 1920. The urine sugar in a case of this kind, which he treated with iodine, dropped from 208 to 71 Gm., while coincidently palpitation and tachycardia were favorably affected. The data recorded in table 2 show how uniformly the administration of compound solution of iodine improves the tolerance in cases of diabetes complicated with exophthalmic goiter. The phenomenon is well illustrated by the following case (chart 1).

15. Labbé, Marcel: Diabete et goitre exophthalmique, Ann. de méd. **7**:95-103, 1920.

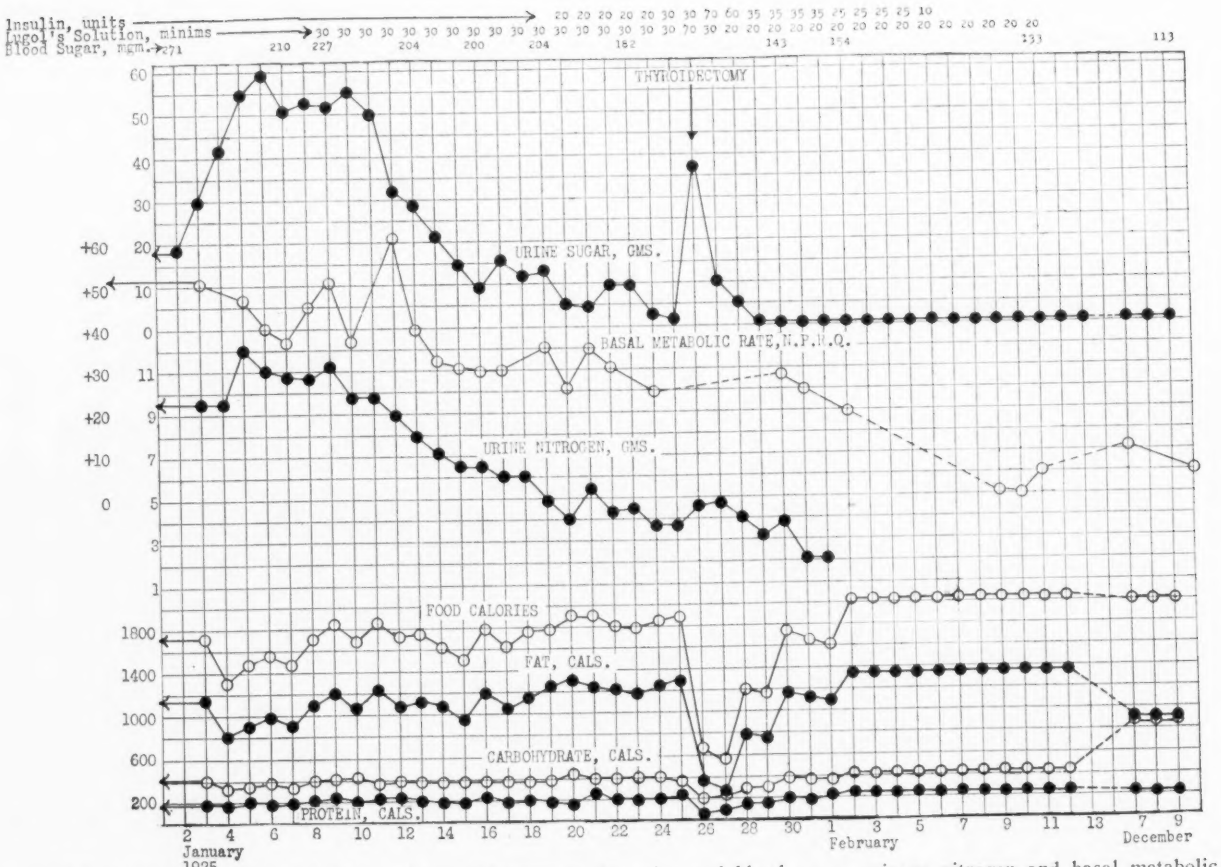


Fig. 1 (case 3).—Effect of iodine and thyroidectomy on the urine and blood sugar, urinary nitrogen and basal metabolic rate in a case of exophthalmic goiter with diabetes mellitus.

CASE 3 (case 5, table 2.)—A woman, aged 43, was admitted Jan. 1, 1925. She had had a nervous breakdown in the spring and had been weak all summer. Definitely recognizable diabetic symptoms, polyuria and polydipsia had been noted in November. Sugar had been found in the urine and a restricted diet had been prescribed. The urine was said to have been sugar free three months before. There was a striking familial record of diabetes, four instances on the maternal side and one on the paternal side.

At the time of admission, the blood sugar was 0.271 Gm. for each 100 cc. The urine contained very little sugar at first, but with a more liberal diet (1,800 calories, glucose equivalent, 120 Gm.) glycosuria increased, and from January 4 to 10 a very constant excretion of about 55 Gm. a day occurred. January 9, a daily administration of 30 minims of compound solution of iodine was started. This was followed by a noticeable diminution in glycosuria which had fallen by January 20 to 6 Gm. Insulin was then given in a dosage of 10 units twice daily and, January 26, thyroidectomy was performed. The pathologist reported hypertrophic parenchymatous thyroid tissue weighing 15 Gm. Large doses of insulin were required for three days following the operation, but subsequently they could be discontinued without recurrence of glycosuria.

This patient was examined again, Dec. 3, 1925. She had adhered to her diet and found no sugar in the urine during the interval. Basal metabolic rates were + 11 and + 6. The carbohydrate in the diet was increased so that the glucose equivalent would be 250 Gm. and still the urine remained sugar free. A test meal of 100 Gm. of glucose was given and the urine contained no sugar, although the blood sugar curve shown in figure 2 is obviously not normal.

THE EFFECTIVENESS OF INSULIN WHEN DIABETES IS COMPLICATED BY HYPERTHYROIDISM

It is well known that when diabetes is complicated by infections the insulin requirement may be materially increased. Similarly when hyperthyroidism is the complication, it is always necessary to use more insulin than would be needed in an uncomplicated case. This is apparent from a perusal of the data given in tables 2 and 4. It is also evident in the course of case 1 (case 9, table 2. March 31, 1925, twelve days after the second admission of this patient, the urine was held sugar free by 90 units of insulin. At this time the diet contained 2,100 calories and had a glucose equivalent of 140 Gm. Discontinuing the administration of iodine was followed by a gradual upward swing of the basal metabolic rate and the excretion of from 10 to 15 Gm. of sugar despite the high insulin dosage. The resumption of the daily dose of iodine was followed in time by a decline of the basal metabolic rate and a reduction of the insulin requirement to 40 units.

THE VALUE OF THYROIDECTOMY IN PATIENTS WITH COMBINED DIABETES AND HYPERTHYROIDISM

While the time elapsed since this group of patients has been under observation is short, the immediate results have been so very satisfactory and the present condition of a large majority of these patients is so encouraging that there can be little question of the value of thyroidectomy for them. When Fitz [6] wrote on this subject he was not encouraged

with the results of operation. Of twelve of his patients with toxic goiter two died immediately after the operation. Several others succumbed to diabetes within the next few years. However, in four of his cases the intensity of diabetic manifestations was very strikingly lessened and apparently life was prolonged. That was in 1920. Since that date the methods of treating diabetes have improved tremendously, due mainly to the great discovery of Banting and McLeod; also the risk of exophthalmic goiter has been distinctly lessened by Plummer's [16] demonstration of the value of iodine in its treatment. The patient with diabetes no longer presents the serious surgical risk that he did. Consequently, he can and should receive the same surgical benefits from thyroidectomy as are available to his less handicapped fellow, provided, naturally, that all the special precautions necessary in his case are taken.

Of the thirty-three patients with hyperthyroidism in this series for whom thyroidectomy was performed, none died as a result of the operation. An improvement in tolerance has occurred within a week or ten days after thyroidectomy in almost every case. In many this improvement has not made it possible or advisable to discontinue the use of insulin. In others it has been so pronounced as to constitute an arrest of the diabetic state. I have quoted the record of one of these in some detail (case 3, chart 1). Thyroidectomy was performed, Jan. 26, 1925, and this was followed in a few days by such a sharp improvement in tolerance that insulin could be discontinued. At a later examination, Dec. 3, 1925, a very rich carbohydrate allowance could be taken without glycosuria being provoked, and a test meal of a 100 Gm. of glucose caused no glycosuria.

There are a number of case reports in the literature of recovery of normal tolerance after thyroidectomy.[17] In none of them, so far as I have been able to find, was the blood sugar determined after glucose test meals. Without such examinations it is scarcely legitimate to claim, as some have done, that an actual cure has followed the removal of the thyroid. Holst [12] reports observations on several instances of persistent glycosuria in two of which glucose test meals after recovery from thyroidectomy failed to cause glycosuria. It is highly probable that these most favorable results merely represent the arrest of a latent diabetic condition. In case 3 there must have been a latent diabetes before hyperthyroidism developed. The familial history speaks strongly for it. This

16. Plummer, H. S., and Boothby, W. M.: The Value of Iodine in Exophthalmic Goiter, J. Iowa State M. Soc. **14**:66-73 (Feb.) 1924.

17. O'Day, J. C.: Diabetes in Association with Toxic Goiter, New York M. J. **111**:815-816 (May 8) 1920. Holst (footnotes 10 and 12). Rohdenburg, G. L.: Thyroid Diabetes, Endocrinology **4**:63-70 (Jan.-March) 1920. Buchanan, J. A.: A Case of Exophthalmic Goiter and Diabetes Mellitus, M. J. & Record **119**:11-13 (Jan. 2) 1924. Rohdenburg, G. L.: A Case of Spontaneous Disappearance of Diabetes, Endocrinology **6**:519-522 (July) 1922.

condition was fanned into life by hyperthyroidism, and when the latter was controlled it subsided again to its original state of latency. Blood sugar determinations made after the glucose test meal (chart 2) were not quite normal, the delayed return to the fasting blood sugar level strongly suggesting the continued presence of diabetes.

MYXEDEMA AND DIABETES

Some of the reputed recoveries of normal tolerance after thyroidectomy may be due to the development of myxedema. In a case reported by Holst [12] diabetes was manifested six months after thyroidectomy for exophthalmic goiter, during a recurrence. Two and one-half years later myxedema appeared spontaneously and then a test meal of 100 Gm. of glucose provoked no alimentary glycosuria. Several instances of myxedema occurring in the course of diabetes and resulting, as in Holst's case, in great amelioration of the tolerance are to be found in the literature. A most interesting example of this was recently seen here.

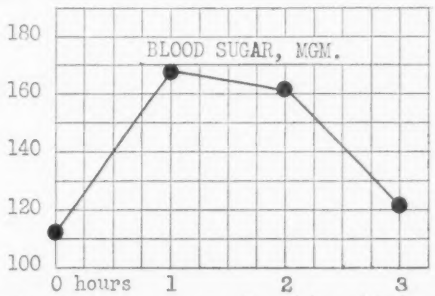


Fig. 2 (case 3).—Blood sugar curve after giving of test meal of 100 Gm. of glucose; the urine contained no sugar.

Case 4.—A male child, aged 7, had been a full term infant with normal health and normal growth up to the age of 15 months. He then manifested polydipsia and polyuria, and sugar was found in the urine. He was placed on a strict diet which, after six months, could be somewhat relaxed without causing a return of glycosuria. Delayed growth and increasing coarseness of the hair led to the diagnosis of hypothyroidism, when he was aged 3. Thyroid treatment was begun but was discontinued because of the return of intense glycosuria and the occurrence of acidosis. During the period of thyroid treatment growth had been resumed. After its discontinuance growth again stopped and the tolerance improved so much that the child "could eat anything without excreting sugar."

On examination at the clinic this patient presented a fully developed picture of juvenile myxedema, the face dull and expressionless, the skin dry and thick, the hair coarse and scanty. Mentality and physical development were much retarded; the height was 38.5 inches, the weight 34 pounds (15.4 Kg.). The basal metabolic rate was — 45. The urine was sugar free; the blood sugar, 0.12 per cent.

There was some difference of opinion among the examining physicians as to whether the child could have had diabetes. My prediction was that when the metabolic rate was raised to normal, diabetes would be evident and insulin would be needed in order to make possible the feeding of a satisfactory diet. Thyroid was

administered in small doses and the metabolism raised very gradually. At the same time the diet was rigidly restricted in carbohydrate and protein. August 2, the basal metabolic rate reached — 10 and sugar appeared in the urine. Later under the reestablished metabolic rates sugar continued to be excreted in amounts as high as 20 Gm. a day, and the fasting blood sugar level reached 0.145 per cent. At the last report, Dec. 29, 1925, the child was gaining in weight and strength but showing sugar despite a rigid diet (glucose equivalent 76 Gm.) and 10 units of insulin daily.

This case lends considerable support to the theory that with lower metabolic rates the tissue cells can utilize a given amount of glucose with less insulin than they require when the metabolism is pitched at a higher rate. The case further indicates that we are not justified in concluding that diabetes has been cured by thyroidectomy unless we can show that the basal metabolic rate has not been reduced below normal in consequence of the operation or of a thyroiditis following operation.

TREATMENT

Thyroidectomy will be clearly indicated in the large majority of cases of combined diabetes and toxic goiter. Nevertheless, the operation should not be undertaken unless the surgeon is familiar with the measures necessary to protect his patient from the effects of the operation. The period of exacerbated toxicity which so frequently follows on the heels of thyroidectomy is extremely dangerous to a patient with diabetes.

In a case of diabetes even greater care should be taken in preparation for thyroidectomy than is necessary with other operations in the presence of diabetes. Normal water balance should be restored, glycosuria and particularly any acidosis should be controlled, and an effort should be made to bring up the general nutrition and to replenish as far as possible the depleted stores of glycogen.[18] The diet of these patients must be richer than is necessary or advisable for other patients with diabetes. The food calories should equal at least twice the normal basal caloric requirement and the allowance of carbohydrate should be fairly liberal (100 Gm. or more). There seems to be no advantage in giving more than 50 or 60 Gm. of protein.

In order to check glycosuria while the liberal diet is being fed, insulin will be required. It is often necessary to inject insulin at six hour intervals. A close watch must be kept to avoid acidosis on the one hand and hypoglycemia on the other. These patients are peculiarly sensitive to the latter, due probably to the fact that the liver in cases of hyperthyroidism may be poor in glycogen.[19]

---

18. Holman, E. F.: Hypoglycemia in Exophthalmic Goiter, Bull. Johns Hopkins Hosp. **34**:69-70 (Feb.) 1923.

19. Richardson, H. B.; Levine, S. Z., and DuBois, E. F.: Clinical Calorimerty: xli. The Storage of Glycogen in Exophthalmic Goiter, J. Biol. Chem. **67**: 737-751, 1926. Sanger and Hun (footnote 3). Holman (footnote 18).

A diagnostic criterion of importance in the coma from hypoglycemia is the blood pressure. This is usually sharply elevated during insulin reactions. I have seen the systolic pressure as high as 220 mm. of mercury during hypoglycemic coma in a patient whose systolic pressure was ordinarily 120. It falls again within half an hour after the blood sugar is restored to normal. So far as I know, this hyperpiesis from insulin has not been reported heretofore. It is due probably to the liberation of epinephrine, a spontaneous attempt at the restoration of a normal blood sugar.[20]

Because of the peculiar sensitiveness of these patients to hypoglycemia it is better not to attempt the complete control of glycosuria until some days after operation. The persistence of traces of sugar in the urine (from 5 to 10 Gm. in a twenty-four hour specimen) seems to have no ill effect either on the resistance of the patient or on the healing of the operative wound.

Compound solution of iodine is given in doses of from 1 to 3 cc. daily: the usual dose is 10 minims (0.6 cc.) three times daily. In cases of adenomatous goiter with hyperthyroidism iodine may be ineffective, but since it is not always possible to exclude exophthalmic goiter and since iodine can do no harm in any case of hyperthyroidism, during the short period while the patient is being prepared for operation, it seems best to use it as a routine when the basal metabolic rate is elevated. If the patient is in diabetic coma and unable to retain medicines given by mouth or by rectum, sufficient absorption of iodine can be secured by painting a 5 per cent tincture of it on the skin. The operation should be deferred until a maximal iodine effect has been obtained and the patient has recuperated as much as possible. This may require from two to three weeks. The criterion of operability in exophthalmic goiter has been discussed recently by Pemberton.[21] Prolonged deep general anesthesia should be avoided. After operation fluids should be given in abundance and sugar (glucose) administered by mouth, by rectum or by vein so that the patient receives 100 Gm. of it daily. The diet can usually be resumed by the second or third day.

If a thyroid reaction results from the operation the doses of iodine and insulin must be increased. It is frequently necessary to give 1 cc.

---

20. Cannon, W. B.; McIver, M., and Bliss, S. W.: The Effect of the Blood Sugar Level on Adrenal Secretion and Sympathetic Activity; A Preliminary Note, Boston M. & S. J. **189**:141-142 (July 26) 1923. Boothby, W. M., and Wilder, R. M.: Preliminary Report on the Effect of Insulin on the Rate of Heat Production and Its Significance in Regard to the Calorigenic Action of Adrenalin, M. Clin. N. Amer. **7**:53-56 (July) 1923. Wilder, R. M.; Boothby, W. M.; Barborka, C. J.; Kitchen, H. D., and Adams, S. F.: Clinical Observations on Insulin, J. Metab. Research **2**:701-728, 1922.

21. Pemberton, J. D.: Present Day Surgical Treatment of Diseases of the Thyroid Gland, J. A. M. A. **85**:1882-1886 (Dec. 12) 1925.

of compound solution of iodine every six hours and to use as much as 20 units of insulin every six hours. The insulin dosage must be controlled by frequent examinations of the urine and blood, as the danger of hypoglycemia seems to be particularly great shortly after the operation.

It is important to give these patients a thorough training in dietetics and in the management of diabetes. The time of their convalescence should be used for imparting this information to them. While diabetes may occasionally be arrested by thyroidectomy and will be decreased in intensity in most cases, it will nevertheless remain after the thyroid element of the combined diseases has been removed. These patients deserve, therefore, the same consideration from the standpoint of diabetes as do others with diabetes.

While there has been no recurrence of hyperthyroidism in this group in which thyroidectomy was recently performed. It is considered advisable before dismissing these patients to caution them against the danger of postoperative recurrence so that they may be prepared to return promptly for further treatment in case thyroid symptoms should manifest themselves anew. In the presence of such recurrence an attempt is made to control the disease with iodine, but if this fails further resection is advisable.

COMMENT

Mention was made in the introductory remarks of studies of the respiratory quotient of patients with toxic goiter, and it was stated that such studies definitely rule out the supposition that the fairly common alimentary hyperglycemia of the patient with hyperthyroidism means diabetes or a true disturbance of carbohydrate metabolism. The phenomena exhibited by patients with true diabetes combined with states of hyperthyroidism or hypothyroidism appear to be definitely related to the general metabolic rate, and therefore are susceptible of explanation without recourse to speculation as to a specific interdependence of thyroid and pancreas.

Fitz suggested that the unfavorable influence of hyperthyroidism in diabetes might be due to the resulting increased rate of total metabolism rather than to any direct effect of the thyroid gland on carbohydrate metabolism. Allen [22] shared this view The idea, as expressed both by Fitz and Allen, was based on the well established observations, particularly those of Allen, that fasting, wasting diseases and other conditions that lower the basal metabolism act favorably on the tolerance of the patient with diabetes, whereas overfeeding which raises the general

22. Allen, F. M.: Studies Concerning Glycosuria and Diabetes, Boston, Harvard University Press, 1913, pp. 842-851; Experimental Studies in Diabetes; Internal Pancreatic Function in Relation to Body Mass and Metabolism; Influence of Thyroid upon Diabetes, J. Metabolic Res. **1**:619-665 (May) 1922.

metabolism acts unfavorably. Boothby and I [7] have pointed out that the influence of heavy protein dietaries in diabetes is much like that of hyperthyroidism in that such diets stimulate the metabolism by their high specific dynamic actions and that as the metabolic rate rises the tolerance falls. Fever, as is well known, elevates the metabolic rate and simultaneously depresses sugar tolerance. Pregnancy does the same to a lesser extent. The action of drugs with a calorigenic influence has thus far not been studied except in the case of thyroxin and epinephrine, both of which lower tolerance.

In general, it appears that all those measures or conditions which stimulate the general metabolism have a depressing action on the tolerance of the diabetic patient similar to that of hyperthyroidism, whereas sedative drugs, such as opium, and conditions which lower the general metabolism act in diabetes like hypothyroidism. I am aware of only one exception to this generalization, namely, exercise. As is well known, muscular work, while raising the rate of heat production enormously, does not provoke a decreased tolerance in diabetes. The reverse may be the case. A number of patients, those who pursue especially arduous labor, such as farming, are provided with two diets, a richer work day diet and a lighter Sunday diet. If they take their work day diet on Sunday they show sugar or require more insulin; if they limit their diet on work days to their Sunday allowance without at the same time reducing their dose of insulin, they develop symptoms of hypoglycemia. This unique position of exercise among factors affecting the metabolic rate is worthy of attention. It suggests that there exists a fundamental difference between the heat production attending muscular contraction and that associated with the chemical processes that are stimulated by food and by calorigenic agents such as thyroxin.

Three facts, that iodine increases the tolerance of diabetic patients with exophthalmic goiter (in which condition it reduces the metabolic rate); that it has no such influence on the tolerance of those diabetic patients with hyperthyroidism due to overfunctioning of adenomatous goiter (in which it does not affect the metabolic rate), and that it has no influence on uncomplicated cases of diabetes, are perhaps the most important contributions of the present study. This evidence is, I think, incontrovertible and strengthens considerably the argument that the rate of the general metabolism governs the efficiency of carbohydrate utilization.

The data thus far presented have shown that the requirement of insulin of patients depending on large doses of the drug is increased by hyperthyroidism. To test this further thyroxin was injected in a patient with very severe diabetes who required a daily injection of 50 units of insulin for a diet with a low glucose equivalent (100 Gm.). This caused

no glucose excretion until after twenty-four hours. In the second twenty-four hours the sugar output was 25 Gm., but by then the basal metabolic rate had been elevated from — 10 to + 23. Also, thyroxin and insulin have been put in solution together and left standing in vitro for seventy-two hours without loss of activity of the insulin. These facts are difficult to explain either on the assumption that the thyroid hormone depresses the pancreas or that the thyroid secretion directly neutralizes insulin. A more probable explanation, in complete harmony with the available clinical and experimental observations, is the following:

The tissue cell, with a metabolism accelerated by thyroxin, requires for a given amount of glucose an amount of insulin that is disproportionately greater than its requirement when its metabolic exchanges are performed at a more leisurely tempo. The higher the metabolic rate the greater is the demand for insulin, even though the total amount of sugar to be utilized in a given time remains constant. The lower the metabolic rate the less the amount of insulin required to do the same work in the same time.

It is possible to suggest several ways by which the apparent insufficiency of insulin in hyperthyroidism might be explained. A simple one that serves at least to correlate the observed facts may be that insulin is more rapidly destroyed when hyperthyroidism exists. The effect of an injection of insulin is short lived at best, from six to twelve hours. The evanescent character of the action of biologic catalysts in general seems to be due to the gradual destruction of such catalysts by the tissues, a destruction attributable to the action on them of catabolic processes. Therefore, it is probable that when oxidations are proceeding at a relatively rapid rate a catalyst, such as insulin, undergoes a more rapid decay, whereas its life may be longer and therefore its efficiency greater when oxidations are taking place more slowly.

Patients with no diabetes, and consequently with large supplies of insulin, reveal no lack of tolerance for carbohydrates, even when their metabolism is stimulated by extreme grades of hyperthyroidism, because their supply of insulin is more than adequate to meet the disproportionately large demands resulting from the accelerated metabolism. In diabetic patients the situation is altered by the fact that the supply of insulin has been limited and a factor of safety, otherwise enjoyed, no longer exists. Therefore, an elevation of the metabolic rate, which in normal persons may be associated with evidence of actual acceleration of carbohydrate metabolism, is attended in the diabetic organism by a paradoxic decrease in carbohydrate metabolism. A diabetic patient with hyperthyroidism is like a man of small means with a wasteful wife. By careful spending both ends might be made to meet, but the squandering of limited resources soon results in disaster.

SUMMARY

This is a study of thirty-eight cases of frank diabetes combined with states of hyperthyroidism and of one case of diabetes associated with myxedema. The association of diabetes and hyperthyroidism occurs with a frequency of about 1.1 per cent of all cases of hyperthyroidism. Exophthalmic goiter is less frequently complicated by diabetes (0.6 per cent of all cases) than adenomatous goiter with hyperthyroidism (2 per cent). The study is not concerned with alimentary glycosuria, which is a much more common phenomenon in cases of hyperthyroidism and does not represent, in my opinion, any actual abnormality of carbohydrate metabolism as herein defined.

The symptoms of hyperthyroidism in a patient with diabetes may be obscured by those of diabetes. This is particularly true in cases with severe acidosis or diabetic coma. It is advisable, therefore, to consider the possibility of hyperthyroidism in all cases of diabetic acidosis.

A mild and possibly inconspicuous diabetes may be fanned into flame by hyperthyroidism, and severe hyperthyroidism (crisis) will readily provoke coma in a diabetic patient.

The requirement of insulin is increased by hyperthyroidism.

Iodine, administered as compound solution in a dosage of from 20 to 60 minims daily to patients suffering from combined exophthalmic goiter and diabetes, reduces the intensity of the diabetes. This effect parallels that on the basal metabolic rate. Iodine has little or no influence on the course of diabetes associated with adenomatous goiter with hyperthyroidism, and is without effect in cases of uncomplicated diabetes.

Thyroidectomy is almost always followed by a considerable gain in tolerance in diabetes complicated by hyperthyroidism. Sometimes this is so great as to suggest an actual cure of diabetes, but the response to glucose test meals may still reveal the persistence of the diabetic tendency. Cure may also be simulated when a hypothyroid state is induced by the operation. A case of juvenile diabetes is cited to illustrate the palliative effect of myxedema developing in diabetes. When the basal metabolic rate of this child was restored to normal the previous diabetic state returned.

Special precautions are necessary when operating on patients with diabetes complicated by hyperthyroidism. The period of exacerbated toxicity which so often follows thyroidectomy is extremely dangerous. There is also considerable danger of provoking hypoglycemia in these patients since they may be peculiarly sensitive to overdoses of insulin. Hypoglycemic coma may be differentiated from other conditions of collapse by the fact that it is usually attended by a striking elevation of the blood pressure.

The phenomena exhibited by patients with diabetes combined with states of hyperthyroidism or hypothyroidism may be related to the general metabolic rate and thus may be explained without recourse to speculation as to a specific interdependence of thyroid and pancreas. It would seem that at lower metabolic rates the tissue cell is capable of utilizing a given amount of glucose with less insulin, and that with higher metabolic rates the requirement of insulin is disproportionately increased.

CARDIAC CAPACITY DETERMINED BY STANDARDIZED EFFORT

PRELIMINARY REPORT *

JOSEPH B. WOLFFE, M.D.
PHILADELPHIA

A method of ascertaining the efficiency of the heart muscle is one of the greatest and most practical problems facing the general practitioner as well as the cardiologist. Late cases of decompensating hearts can be recognized easily. It is the early diagnosis of myocardial insufficiency that is of great value, for it is only at that stage that proper management may allay and frequently prevent decompensation. It would be a great error to recommend any one single method of investigation on which judgment may be based. Since the heart is one of the most susceptible indexes of health and mirrors the state of many other organs, it would be amiss to dissociate the study of the cardiovascular mechanism from the rest of the body; therefore, one must follow the accepted routine method of investigation in order to arrive at a fairly accurate diagnosis. Hence, a complete cardiovascular study should include a thorough history, a physical examination, roentgen-ray, electrocardiographic and polygraphic records, blood pressure and, last but by no means least, the cardiac response to effort.

Because of the present widespread conception that the electrocardiograph is the most infallible guide to the diagnosis of heart conditions, it is well to emphasize the fact for the benefit of those who are not acquainted with the instrument that it serves only as an adjunct, and although most valuable in recognizing disturbances in conductivity, it cannot in any way replace the previously mentioned methods of investigation. It is an accepted fact that frequently advanced pancardial changes electrocardiographically fail to show any appreciable abnormality.

Patients with injured hearts often present few signs on the usual physical examination while, on the other hand, some with marked abnormal physical signs recover without any treatment, or after reaching their three score and ten "die with it, but not of it." In the light of our present knowledge, we fully realize that it is not the extent of an endocardial lesion, or the loudness of a murmur, or the type of arrhythmia that is the determining factor of the actual state of the heart, but the condition of the heart muscle, its ability to stand up

* The response to exercise may be said to depend not only on the heart but also on the condition of the blood vessels, so that in speaking of the "cardiac response to exercise" we use the term "cardiac" as referring not only to the heart but also to the entire cardiovascular system.

under the load of daily physical strain; in other words, it is the amount of cardiac reserve force.

After much experience and careful thinking, Sir Thomas Lewis, a great investigator and able teacher, writes as follows: "Had systolic murmurs and modifications of the heart sounds never been discovered, the practice of medicine would have stood on a much higher plane than it does today." He regards the latter signs, and properly so, only as hints or guides to possible local mischief, but certainly does not attach the degree of importance that apparently is given them by the greater number of practitioners today.

One is greatly impressed with the fact that even in the earlier works of Sir James Mackenzie, he constantly lays stress on the condition of the heart muscle and the amount of reserve force as a guide to the prognosis. The relation between the cardiac force utilized during the hours of usual activity and the reserve force, which is called on only when additional strain is applied, is an important one. It seems rational to think that any early cardiac pathologic condition which is not compensated for will diminish proportionately the cardiac reserve force. Hence, any simple and accurate method by which the latter could possibly be determined should prove to be of untold value.

Numerous tests have already been described by various investigators, many of which are practical with certain limitations. The hopping test, which is used a great deal, varies greatly with the individual, with his mental attitude and his cooperation. Many will not take it seriously, but consider it more or less as a joke; hence, the cooperation of the patient is poor and the importance and value of the test are greatly diminished. Furthermore, such a test is not applicable in all cases; i. e., a stout person would be at obvious disadvantages other than those which might justly be attributed to a myocardial condition.

Running, swinging of dumb bells, lifting of weights, moving stairways, ergostats, stationary bicycles and other tests are subject to similar criticism. Still, these are valuable in ascertaining the cardiac reserve force, provided the same test is repeated at intervals and the progress observed.

INSTRUMENT FOR TESTING CARDIAC CAPACITY

It seems apparent that there is still room for a mechanism constructed for the purpose of subjecting a person to a predetermined amount of work and for a device connected with the mechanism for recording the work done. In this way the person may be subjected to the same amount of work or more, if desired, at different intervals of time. It is also important that the mechanism should be reliable and simple enough to be within the reach of any practitioner. The instrument I am about to describe is a simple embodiment of these features.

My belief in its reliability is based on the numerous experimental data compiled by my associates and myself, as well as on the fact that an apparatus of the same order has been, and still is, the most frequently used work measuring device of engineers all over the world.

The salient features of the machine are shown in figure 1. A pulley is keyed to the shaft, which is rotated by the person to be exercised by means of handles rigidly connected to the shaft, as shown.

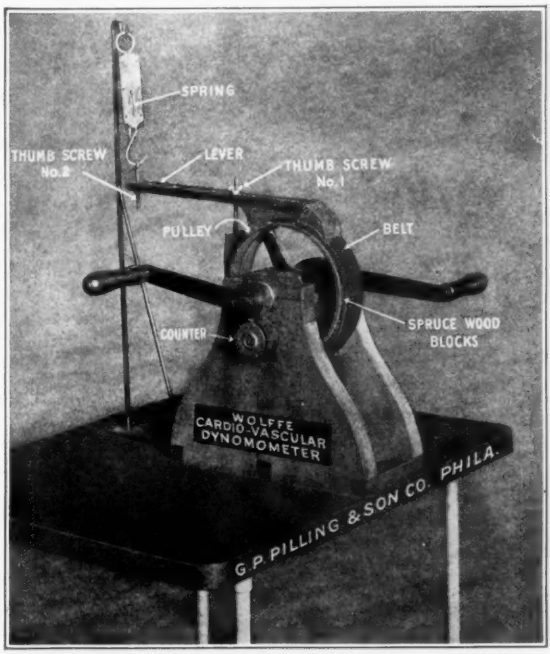


Fig. 1.—Cardiovascular dynomometer. Although this figure represents the machine I use, I am making many refinements at the present time, in conjunction with the George P. Pilling & Sons Company, which will greatly improve this model but not alter its general aspect.

The shaft revolves in bearings conveniently placed in the frame. A friction member, which is made up of a belt studded with wooden blocks, encircles the pulley. Blocks made of spruce wood have been found to give the best results. One end of the belt is nailed to the arcuate part of the lever while the other end carries a screw which fits into a perforation in the lever, thumb screw 1, and is held there by means of a thumb nut, thus giving the wide range of friction between the belt and the pulley.

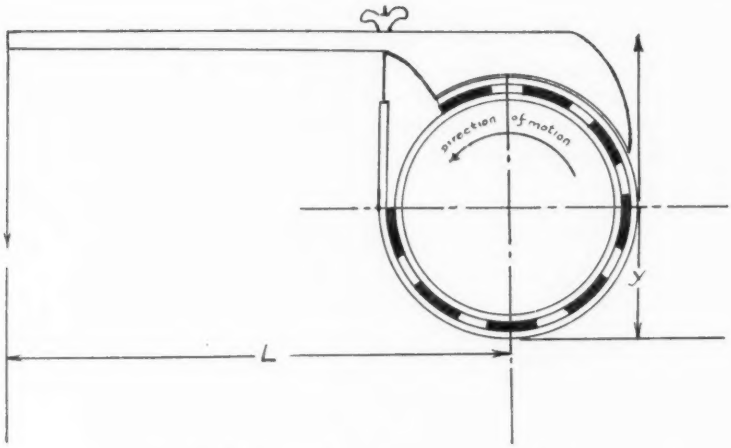


Fig. 2.—Cardiovascular dynomometer work chart.

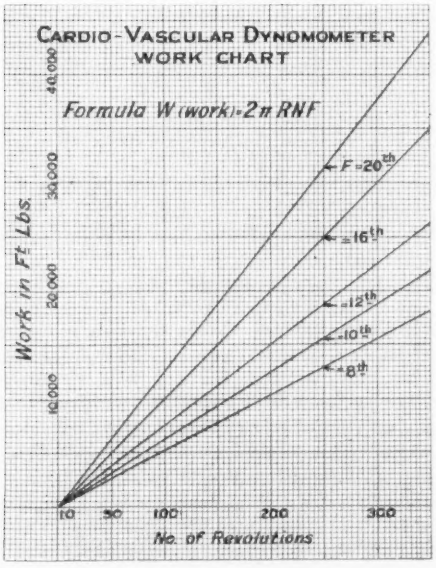


Fig. 3.—Work Chart

The friction between the belt and the pulley would ordinarily cause the belt and lever to turn together with the pulley. To keep the belt from turning, I connect the free end of the lever by means of a thumb nut, thumb screw *2*, to the rigid scale, as shown. The scale is thus made to function as a measuring device of the force necessary to overcome the friction between the belt and the pulley, since it is evident that the tighter the belt is clamped down on the pulley, the greater

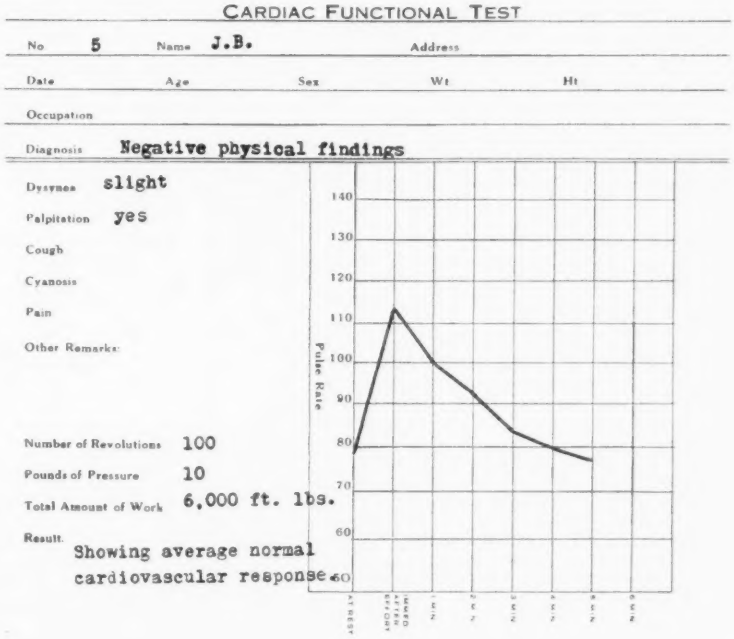


Fig. 4.—Average functional response of 1,000 normal persons.

will be the force necessary to keep the belt from turning with the pulley. As the tension of the belt is increased, the force registered will be increased; this causes the scale to be elongated, which in turn tilts the lever from its horizontal position. I compensate for this tilting by drawing thumb screw *2*.

Thus far we have means for subjecting the person to be exercised to a predetermined strain while doing work. A established formula may be used. The derivation of this formula may be seen from figure *2*.

Y indicates the radius of the pulley in feet; Z, the frictional force in pounds between the pulley and the blocks; F, the force in pounds recorded on spring balance; L, length of the brake arm in feet. For the condition of equilibrium, i. e., "horizontability" of the brake lever arm and by the law of moments for equilibrium, $Z \times Y = F \times L$ (1).

In one revolution, the frictional force Z is overcome through a distance equal to the circumference of a circle with a diameter $2Y$, i. e., $2 \pi Y$.

Hence, the work done in foot pounds during one revolution is $2 \pi ZY$ (2).

In n revolutions, the work done in foot pounds will be $2 \pi ZY n$ (3).

CARDIAC FUNCTIONAL TEST

No. 2 Name D.G. Address

Date 2-13-25 Age 24 Sex male Wt 145 Ht

Occupation

Diagnosis Myocardial degeneration (arteriosclerotic).

Dyspnea marked and prolonged (2 min.)

Palpitation marked

Cough slight

Cyanosis --

Pain slight precordial pain

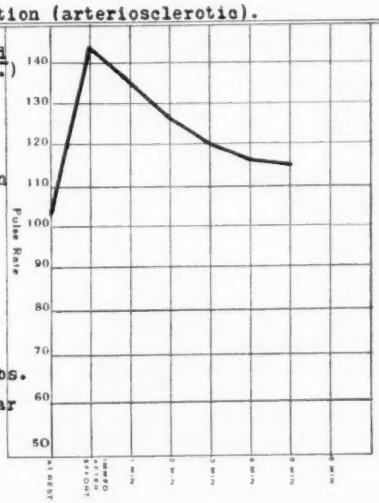
Other Remarks fatigue

Number of Revolutions 50

Pounds of Pressure 12

Total Amount of Work 3600 ft. lbs.

Result Impaired cardiovascular response to effort.



Subsequent Tests

Fig. 5.—Functional response in case of myocardial degeneration (arteriosclerosis).

This formula could be readily employed provided some means could be used to obtain the frictional force Z. But according to equation 1, the relation between ZY and FL is given as $ZY = FL$. Substituting the relation in equation 3, we have $2 \pi Fln$ and the formula to be used.

For a given machine, the constants 2π and L can be combined in one constant k; thus the formula becomes

$$\text{Work (foot pounds)} = kFn.$$

Further, if the value of F is kept constant, it can again be combined with the other constant k to form a new constant K. The formula then becomes

$$\text{Work (foot pounds)} = Kn.$$

This allows us to draw a chart (fig. 3) with F as the ordinate and n as the abscissa on which the work done can be ascertained. If the force is kept constant, without resorting to calculation, curves for a number of different forces may be drawn on the same chart. Three such curves have been found sufficient in ordinary practice.

To determine the number of revolutions the person exercised has turned, I use the counter, actuated by a cam key to the shaft. The

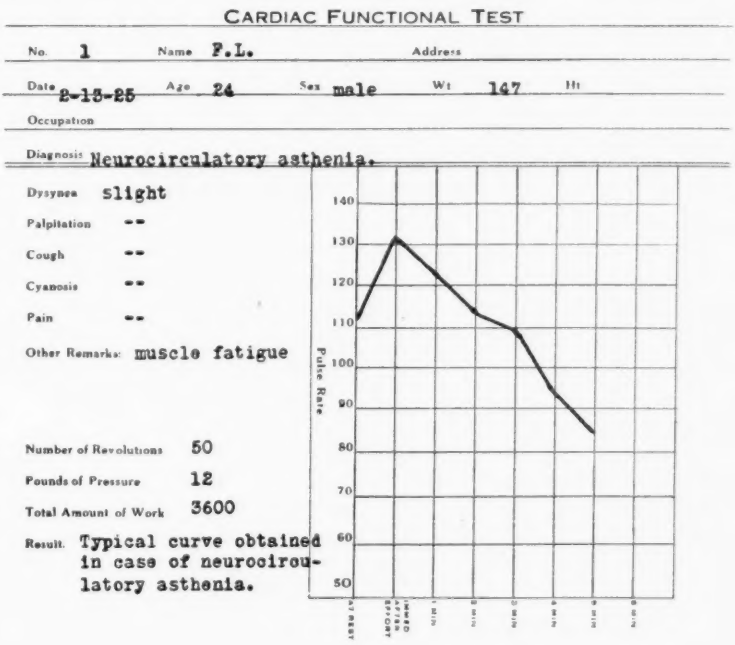


Fig. 6.—Functional response in a case in which there was much impaired cardiac reserve, showing the improvement in cardiac efficiency after adequate convalescent care.

rate at which the work is done can be regulated either by an attendant, who keeps time for the patient, or by means of a metronome, which has been found to be easily followed by the person exercised, and its use is conducive to much better results. If a metronome is used, the counter may be dispensed with since it is easy to obtain the number of revolutions, knowing the time the person was subjected to exercise;

i. e., if the metronome is set for thirty revolutions a minute, then the number of minutes exercised multiplied by the number of revolutions a minute gives the total number of revolutions. This may be done mentally, and the procedure of finding the work done is shown in figure 3.

Work, from a physicist's point of view, is the overcoming of a force through a distance, and is measured by the product of the force

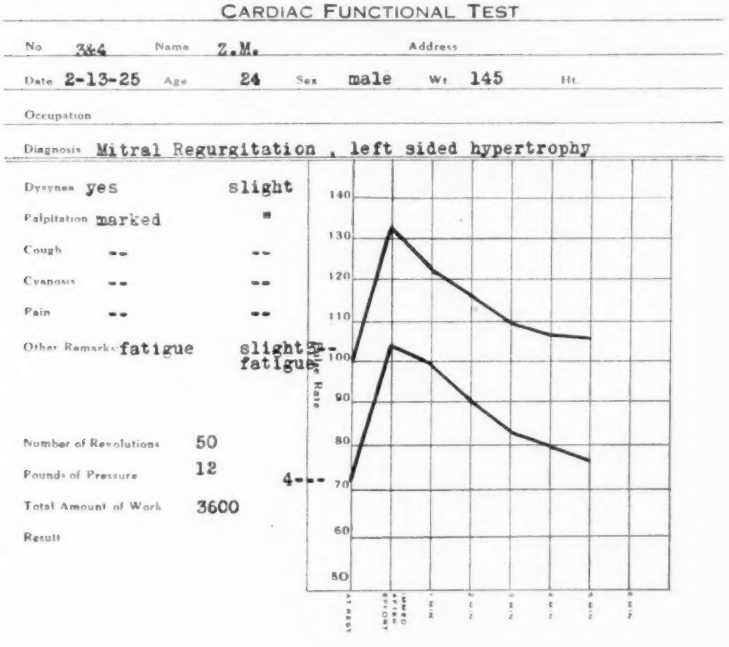


Fig. 7.—Functional response in case of mitral regurgitation and left sided hypertrophy.

and the distance through which the force is overcome. With this instrument on hand, one can estimate the cardiac efficiency by the method either of Graupner or of Mendelsohn:

(*a*) The Graupner method consists of taking the blood pressure before exercise and taking it again immediately after and at intervals until it returns to its preexercise pressure. (*b*) The Mendelsohn

method, which we are using, consists of first taking the pulse while the patient is at rest. The patient is then subjected to a certain amount of work, individualized according to his age and physique. The pulse is taken again immediately afterward and at one minute intervals until it returns to its preexercise rate. After exercise the pulse rate is found to be elevated in every case, and if it is assumed the better the myocardium the sooner the pulse will return to normal, deductions can be made from the test as well as from similarly applied tests at subsequent comparative examinations.

Figure 4 shows the average response obtained in testing 1,000 normal persons.

Figures 5 and 6 illustrate the functional responses of persons of similar age and physique, but with different cardiac conditions, each showing a pulse record and symptomatic response frequently seen in the type of heart which it represents.

I should like to mention a few important clinical applications that this instrument would have for every practitioner:

1. The instrument would be a valuable adjunct in the diagnosis of myocardial degeneration. A patient with a poor myocardium is able to do only a comparatively small amount of work before he develops the characteristic symptoms of dyspnea, palpitation and precordial oppression.

2. If the amount of work required to produce these symptoms is noted at the first examination, the amount of work done at subsequent examinations before the onset of dyspnea, palpitation, etc., would determine the increase or decrease in myocardial power. This record is a valuable aid in determining the arrest or progress of the disease.

CONCLUSIONS

The practical determination of the efficiency of the myocardium is of paramount importance to every practitioner.

Such methods as foot hopping and dumb bell swinging have proved unsatisfactory, and the results are often misleading. Moreover, no one of these tests is applicable to all patients, nor is the information obtained conducive to the keeping of accurate records.

The use of an instrument such as that described above fulfils the requirements of simplicity in that it can be operated by a novice, and it is practicable in that the data obtained are of inestimable value in determining the cardiac efficiency of the patient, and records can be kept of the first and subsequent examinations.

Systematic use of the records obtained has proved an accurate guide in noting the progress of the disease.

As the patient improves and is able to perform more work without the production of symptoms, we have an indication to show him that he is convalescing. The encouragement this has produced is remarkable.

THE BASAL METABOLISM IN BERIBERI *

SEIZABURO OKADA
AND
EIICHI SAKURAI
TOKYO, JAPAN

The basal metabolism in beriberi was quite unknown until recent years. A systematic investigation on this problem was first attempted by us. The preliminary report [1] was published at the same time as that of the basal metabolism of the Japanese, reported in a previous article. The conclusion was that the main part of beriberi shows a normal basal metabolic rate, except that in some cases, especially when paralysis or atrophy develops, a marked diminution is also to be observed.

Fleming [2] studied the respiratory metabolism and blood chemistry of Filipinos and concluded that between two groups of Filipinos, one with a confirmed diagnosis of beriberi, the other surgical convalescents, no essential differences were found in the basal metabolism rate, respiratory quotient or blood chemistry.

As to the vital cause of beriberi, the opinions of various investigators are still diverse. Some workers attribute this disease to the effect of vitamin B deficiency, which seems most plausible, but this opinion has met strict contradictions. Therefore, it seems better to deal with this disease alone and not to touch on the vitamin deficiency disease in this article to avoid confusion.

OBSERVATIONS AND TECHNIC

The patients here studied were mostly outpatients and only some were ward patients. In all cases the symptoms had sufficiently developed to make a confirmed diagnosis of beriberi. The cases with complications or in which there were other diseases were carefully excluded. Some of the patients had already changed their usual dietary habits or were treated with medicines, while others were quite new patients who had not received treatment and who continued their usual nourishment and general habits of life (cases 16, 18, 30, 32, 33, 39, 41, 43 and 44).

The measurements were made by the method reported in the previous paper as used on normal subjects.

RESULTS

Physical Characteristics.—The patients studied were all males ranging in age from 15 to 29, of whom twenty-two were from 15 to 19 and

* From the medical clinic of Prof. R. Inada, Imperial University of Tokyo,

1. Okada, S.; Sakurai, E.; Ibuki, T., and Kabeshima, H.: Ikai Jiho no. 1479, Nov. 4, 1922; Japan M. World **3**:102 (May) 1923.

2. Fleming, W. D.: J. Metab. Research **4**:105, 1923.

twenty-five from 20 to 29. The average height of the first group was 157.6 cm. and of the second, 157.6 cm. The average weight was 51.5 and 54.5 Kg., respectively. The average weight of the patients more than 20 years of age was therefore much greater than that of normal subjects (2.65 Kg., 5.1 per cent) notwithstanding the fact that the average height of the former was somewhat less than that of the latter (4.3 cm., 2.6 per cent), a fact that may be attributed to the edema of the patients. The average surface area according to the Du Bois height-weight factors was 1.5 for the young patients and 1.54 square meters for the adults.

Clinical Observations.—Blood Pressure: All the ward patients were repeatedly examined. The systolic pressure ranged from 123 to 90 mm., the average being 107 mm., the diastolic pressure from 65 to less than 40 mm., so that it was often not measurable. The persistently low diastolic pressure with normal systolic pressure is the characteristic feature in beriberi. The pulse pressure was therefore usually greater than 50 mm. and the celerity of the pulse usually was significant. With the decline of the disease the diastolic pressure rises after a while to the normal height.

Pulse Rate: The pulse rate ranged from 50 to 120, the average being 77, which is distinctly higher than the average of normal subjects. In general when cardiovascular symptoms prevail, the pulse rate is high and especially when it threatens heart incompetence.

Respiration Rate: The respiration rate was from 10 to 29, the average being 19, which is also distinctly higher than the normal value of 13. No parallelism between pulse rate and respiration rate is to be found.

Temperature: The body temperature was from 35.6 to 37.4 C., in most cases being under 37 C. The climate, when the determinations were performed, was relatively hot, from May to October. This happened naturally as beriberi prevails in Japan in these seasons.

Heart: The area of dulness of the heart was enlarged in most cases to both the right and the left side; roentgenologically and by pathologic anatomy this is proved to be due especially to the dilatation and hypertrophy of the right ventricle and auricle, with more or less marked accompaniment of the left. At the apex and at the left sternal margin the first sound was often hollow or a systolic murmur was recognized. The second pulmonic sound was almost always more or less accentuated. The crural and brachial sounds or murmurs were more or less pronounced.

Edema: In most cases more or less edema was recognized, especially at the tibial edge, less often at the back of the foot. Pronounced general edema was in no case observed though creeping dropsy (not

TABLE 1.—*Metabolism Data in Beriberi Patients* *

Case	Age	Date	Height in Cm.	Weight in Kg.	Surface Area (Du Bois Height-Weight Formula) Sq. Meters	Pulse Rate	Respiration Rate	Carbon Dioxide per Minute	Oxygen per Minute	Respiratory Quotient	Calories for Each 24 Hours	Calories per Square Meter per Hour (Du Bois)	Basal Metabolic Rate: Du Bois Standards, per Cent	Basal Metabolic Rate: Harris and Benedict Standards, per Cent	Body Temperature, C.
1	15	5/25/22	156.2	48.9	1.46	80	29	184	247	0.74	1,678	47.9	+ 4.1	+18.2	36.5
		6/ 1/22	.....	47.8	1.45	90	21	197	244	0.81	1,670	48.0	+ 4.3	+18.9	36.6
2	21	6/ 3/22	156.8	50.6	1.49	72	18	163	202	0.81	1,395	39.0	— 1.3	— 0.7	37.0
		6/ 7/22	.....	....	1.49	75	15	177	211	0.84	1,466	41.0	+ 3.8	+ 4.3	....
		6/ 9/22	.....	....	1.49	80	14	161	204	0.79	1,409	39.4	— 0.2	+ 0.3	....
3	27	8/ 1/22	146.2	46.3	1.36	84	15	150	197	0.76	1,332	40.8	+ 3.3	+ 6.4	35.8
		8/ 3/22	.....	47.2	1.37	82	16	154	185	0.83	1,289	39.2	— 0.8	+ 1.9	35.8
4	16	8/ 1/22	152.3	44.0	1.37	78	18	173	187	0.92	1,328	40.4	—12.2	+ 0.2	36.0
		8/ 4/22	.....	44.6	1.38	66	17	169	190	0.90	1,351	40.8	—11.3	+ 1.3	36.2
5	22	8/14/22	156.6	66.8	1.67	50	21	146	173	0.84	1,214	30.3	—23.3	—24.1	....
		8/16/22	.....	66.5	1.67	58	19	160	187	0.85	1,310	32.7	—17.2	—18.7	35.6
		8/22/22	.....	64.3	1.64	56	29	151	178	0.85	1,240	31.5	—20.2	—21.5	....
6	16	8/ 9/22	161.0	54.7	1.57	66	20	182	206	0.88	1,451	38.5	—10.5	— 4.3	36.5
		8/12/22	.....	53.2	1.54	60	28	183	193	0.94	1,401	37.9	—11.9	— 6.4	36.1
		8/16/22	.....	53.8	1.54	64	21	180	193	0.93	1,397	37.8	—12.1	— 7.1	36.1
7	24	9/ 4/22	158.5	47.8	1.43	84	23	161	204	0.79	1,411	41.1	+ 4.1	+ 6.1	36.4
		9/ 5/22	.....	47.4	1.42	84	23	148	206	0.72	1,394	40.9	+ 3.2	+ 5.3	36.4
8	25	9/ 6/22	158.5	58.3	1.59	100	22	170	225	0.76	1,523	39.9	+ 1.0	+ 2.1	36.4
9	18	9/ 6/22	163.0	53.5	1.57	105	21	144	183	0.79	1,266	33.6	—18.0	—15.4	36.2
		9/10/22	.....	54.4	1.57	100	16	168	175	0.95	1,255	33.3	—18.8	—16.9	36.6
10	21	9/ 8/22	169.5	57.0	1.66	84	20	179	233	0.77	1,570	39.4	— 0.1	+ 0.8	36.8
11	18	9/19/22	159.0	57.1	1.61	60	19	149	181	0.82	1,308	41.6	+ 1.4	+ 4.5	36.6
12	19	9/21/22	160.5	45.5	1.45	66	22	212	218	0.97	1,569	45.1	+10.0	+14.8	36.6
13	24	9/25/22	153.0	45.3	1.39	90	14	155	191	0.81	1,321	39.6	+ 0.2	+ 2.2	36.5
		9/28/22	.....	44.6	1.38	60	18	151	181	0.83	1,255	37.9	— 4.0	— 2.2	36.0
14	17	9/29/22	161.0	54.8	1.57	88	23	196	236	0.83	1,643	43.6	+ 1.4	+ 8.7	36.7
		10/ 1/22	.....	55.5	1.58	60	20	189	224	0.84	1,566	41.3	— 3.9	— 0.9	36.2
15	17	9/30/22	159.0	50.2	1.50	60	18	168	202	0.83	1,411	39.2	— 8.6	— 1.8	36.0
		10/ 4/22	.....	49.6	1.49	64	15	166	185	0.90	1,309	36.6	—14.9	— 8.4	36.3
16	16	10/ 8/22	163.3	66.1	1.72	68	21	205	256	0.80	1,771	42.9	— 0.2	+ 5.2	36.4
		10/ 9/22	.....	66.3	1.72	68	31	220	273	0.81	1,693	42.7	— 0.7	+ 0.3	36.8
17	22	9/22/22	161.5	55.3	1.57	68	15	175	208	0.84	1,447	38.4	— 2.8	— 5.2	36.2
18	18	10/25/22	156.5	54.6	1.53	110	13	169	223	0.76	1,531	41.3	+ 0.7	+ 3.5	36.5
		10/27/22	.....	53.5	1.52	90	11	165	219	0.75	1,492	40.9	— 0.2	+ 1.9	36.4
19	19	11/ 2/22	152.0	44.6	1.38	84	19	162	230	0.70	1,543	46.6	+13.6	+17.6	36.5
		11/ 3/22	.....	44.6	1.38	98	16	152	222	0.70	1,497	45.2	+10.2	+14.1	36.4
		11/ 4/22	.....	44.7	1.38	90	18	161	209	0.77	1,437	43.4	+ 5.8	+ 9.4	36.5
20	21	11/16/22	155.0	54.7	1.52	90	16	178	226	0.79	1,550	42.5	+ 7.6	+ 6.7	36.5
		11/17/22	.....	54.3	1.52	78	17	156	227	0.70	1,521	41.7	+ 5.1	+ 5.1	36.9

21	26	11/23/22	159.0	56.3	1.56	94	19	192	270	0.71	1,808	48.3	+22.3	+23.7	36.7
		11/24/22	.....	56.4	1.57	53	21	190	238	0.80	1,639	43.5	+10.2	+12.1	36.5
		11/25/22	.....	56.4	1.57	104	24	192	287	0.67	1,895	50.3	+27.3	+29.6	36.6
22	17	5/10/23	150.5	47.3	1.45	90	20	173	210	0.82	1,462	42.0	− 2.3	+ 7.9	36.3
		5/12/23	.....	47.2	1.45	87	19	163	196	0.83	1,364	39.2	− 8.8	+ 0.7	36.5
23	20	5/25/23	155.0	64.5	1.63	78	25	198	249	0.79	1,710	43.7	+ 6.6	+ 7.3	35.9
24	21	7/19/23	167.5	60.9	1.69	64	23	167	223	0.75	1,521	37.5	− 5.1	− 4.9	36.8
		7/20/23	.....	61.2	1.69	61	23	178	197	0.90	1,407	34.7	−12.1	−12.3	36.4
25	26	7/19/23	161.5	60.3	1.64	55	21	187	206	0.81	1,468	37.3	− 5.6	− 3.9	36.5
		7/21/23	.....	58.9	1.63	49	19	193	217	0.89	1,522	38.9	− 1.5	+ 0.8	....
26	22	7/19/23	149.5	52.5	1.46	90	19	219	268	0.82	1,843	52.6	+33.1	+32.9	37.3
		7/20/23	.....	51.8	1.45	82	19	190	198	0.96	1,439	41.1	+ 4.0	+ 3.7	37.4
		7/21/23	.....	51.5	1.45	72	23	171	159	0.96	1,284	36.9	− 6.6	− 6.5	36.8
27	19	7/22/23	165.5	60.7	1.67	108	18	222	234	0.95	1,679	41.9	+ 2.2	+ 4.9	37.3
		7/23/23	.....	60.3	1.67	86	14	203	250	0.81	1,735	43.3	+ 5.6	+ 8.8	36.6
28	19	7/26/23	162.0	54.6	1.57	76	23	162	228	0.71	1,537	40.8	− 0.5	+ 2.4	36.5
29	21	7/26/23	162.2	54.3	1.57	78	22	141	208	0.71	1,394	37.0	− 6.3	− 6.0	36.5
		7/27/23	.....	54.9	1.57	72	19	175	211	0.83	1,387	36.8	− 6.8	− 7.0	36.4
30	23	7/26/23	156.5	49.8	1.48	76	20	191	206	0.93	1,471	41.4	+ 4.8	+ 6.7	36.7
		7/27/23	.....	49.2	1.47	64	18	165	210	0.79	1,461	41.4	+ 4.8	+ 6.5	36.0
31	23	7/29/23	159.3	60.2	1.62	68	13	182	216	0.84	1,506	38.7	− 2.0	− 2.6	36.0
		7/30/23	.....	59.8	1.61	63	14	178	211	0.84	1,484	38.4	− 2.8	− 3.0	36.3
32	21	7/29/23	152.5	48.5	1.43	80	19	156	192	0.81	1,328	38.7	− 2.0	− 2.0	37.0
		7/30/23	.....	48.6	1.43	77	15	155	191	0.81	1,318	38.4	− 2.8	− 2.8	36.6
33	19	8/ 2/23	159.0	58.0	1.59	60	21	179	214	0.83	1,496	39.2	− 4.5	+ 2.3	36.7
34	23	8/ 3/23	155.5	53.1	1.51	74	14	164	206	0.80	1,421	39.2	− 0.7	+ 0.3	36.9
35	16	8/ 2/23	150.5	46.7	1.39	114	16	158	222	0.71	1,491	44.7	− 0.7	+10.1	37.3
		8/ 3/23	.....	46.6	1.39	88	16	154	217	0.71	1,465	43.9	− 4.5	+ 8.3	36.8
36	29	8/ 5/23	162.0	55.7	1.59	86	15	183	256	0.71	1,729	45.3	+14.6	+19.4	36.9
		8/ 6/23	.....	55.6	1.59	60	12	166	235	0.71	1,587	41.6	+ 5.3	+10.0	36.4
37	23	8/ 5/23	162.7	51.6	1.54	120	16	188	253	0.75	1,722	46.6	+17.9	+20.0	37.4
		8/ 6/23	.....	51.4	1.54	80	15	180	237	0.76	1,623	43.9	+11.4	+13.3	36.8
38	20	8/ 9/23	159.5	55.2	1.56	108	25	208	265	0.79	1,820	48.6	+18.5	+22.3	37.0
		8/10/23	.....	54.1	1.55	110	26	218	265	0.82	1,841	49.5	+20.7	+24.9	37.0
39	19	8/ 9/23	160.0	53.3	1.54	76	20	172	232	0.74	1,571	42.5	+ 3.6	+ 6.7	36.4
40	22	8/ 9/23	154.5	44.1	1.39	67	18	163	194	0.84	1,348	40.4	+ 2.3	+ 3.9	36.8
		8/10/23	.....	43.7	1.38	60	17	163	192	0.85	1,344	40.6	+ 2.7	+ 4.0	36.5
41	23	8/10/23	158.0	64.7	1.66	80	22	206	226	0.91	1,606	40.3	+ 2.0	+ 0.9	36.5
42	18	8/12/23	154.5	50.6	1.47	67	19	176	251	0.70	1,693	48.0	+11.6	+19.7	36.3
		8/13/23	.....	50.2	1.47	60	18	158	227	0.70	1,524	43.2	+ 0.5	+ 8.2	37.1
43	26	8/12/23	155.5	59.5	1.58	76	16	185	247	0.75	1,684	44.4	+12.4	+21.4	36.6
44	19	8/12/23	145.5	41.7	1.29	77	20	167	186	0.89	1,313	42.4	+ 3.4	+ 5.9	36.8
		8/13/23	.....	41.7	1.29	74	19	151	174	0.87	1,226	39.6	− 3.4	− 1.1	36.1
45	18	8/30/23	165.0	55.2	1.60	54	11	213	217	0.98	1,574	41.0	− 4.6	+ 2.9	36.5
		8/31/23	.....	54.6	1.60	52	13	201	214	0.94	1,536	40.0	− 7.0	+ 0.9	36.3
46	19	8/30/23	149.5	57.1	1.39	69	10	189	203	0.93	1,448	43.4	+ 5.8	+ 8.5	37.1
47	19	8/30/23	159.2	56.1	1.57	74	19	204	230	0.89	1,620	43.0	+ 4.9	+ 7.5	36.9
		8/31/23	.....	56.0	1.57	61	20	208	234	0.89	1,654	43.9	+ 7.1	+ 9.9	36.9

* All males.

TABLE 2.—*Main Clinical Aspects*

Case	Heart: Right Border (Absolute Dulness)	Heart: Left Border (Absolute Dulness)	Heart: Accentuation of the Second Pulmonic Sound	Crural Sound	Edema	Knee Jerks	Achilles Reflexes	Hypesthesia	Remarks
1	Right sternal margin	Nipple line.....	+	Murmur +	+	—	—	Legs +	Paralysis of legs ++; tenderness of calf mucles +; Chaddock +
2	Normal.....	Normal.....	+	Murmur +	+	—	—	Legs +	Paralysis of legs +; tenderness of calf muscles +; cyanosis +
3	Midline.....	Just inside of nipple line	+++	+++	+	—	—	Legs +, lips +	Brachial sound +; cyanosis +; main diet, rice; August 17, died of heart incompetence
4	Left sternal margin	Nipple line.....	+++	+++	++	—	—	Legs +, right hand +, abdomen +	Brachial murmur +; weakness and numbness of legs +
5	Midline.....	Half finger inside of nipple line	—	—	—	Normal	Normal	Legs +, hands +	Tenderness of legs +++; numbness of lips and legs +; urine: protein trace, indican +
6	Midline.....	Inside of nipple line	+, divided	+++	—	Very active	Active	Legs +	Brachial sound weak; numbness of legs and arms ++; urine; indican +
7	Right sternal margin	Just inside of nipple line	—	++	—	—	—	Legs +	Brachial sound weak; paresthesia +; weakness and numbness of legs +; palpitation +; tenderness of calf muscles +
8	Right sternal margin	Nipple line.....	+	++	++	—	—	+	Brachial sound +; numbness of legs +; urine: protein, trace
9	Right sternal margin	One finger outside of nipple line	+++	++	++	—	—	Legs +	Tenderness of calf muscles +; weakness of legs ++
10	Midline.....	Nipple line.....	++	+++	+++	—	—	+	Paresthesia +; paralysis +; Chaddock +
11	Midline.....	Inside of nipple line	+	+	—	—	—	+++	Numbness and paralysis of legs ++
12	Normal.....	Normal.....	+++	++	+	—	—	Legs +, finger +	Brachial murmur +; tenderness of calf muscles +; numbness of legs +
13	Normal.....	Normal.....	+++	++	+	—	—	Legs +	Paresthesia +
14	Normal.....	Nipple line.....	+	++	+++	Very active	Very active	Legs +	Numbness and weakness of legs +; tenderness of calf muscles +; Chaddock +
15	Midline.....	Inside of nipple line	+	+	++	—	—	Legs +	Numbness of legs +; tenderness of calf muscles +
16	Midline.....	Just inside of nipple line	+	+	+++	Active	Active	+	Tenderness of calf muscles +; Chaddock +
17	Midline.....	Just inside of nipple line	++	+	+	Very active	Very active	Legs +	Paresthesia +; tenderness of calf muscles +; Chaddock +
18	Midline.....	Nipple line.....	+	+++	+++	—	—	Legs +	Brachial sound +; palpitation and dyspnea on movement +
19	Midline.....	Nipple line.....	++	++	++	—	—	Legs +	Paresthesia +
20	Midline.....	Nipple line.....	+	Murmur +	+++	—	—	Legs +	Tenderness of calf muscles +; Chaddock +
21	Midline.....	Somewhat outside of nipple line	++	+	++	—	—	Legs +	Numbness and paresthesia of legs +

22	Right sternal margin	Just inside of nipple line	+	Murmur +	++	Normal	Normal	Legs +	Numbness of legs +; tenderness of calf muscles +; urine: protein, trace; indican +
23	Midline.....	Nipple line.....	++	Murmur ++	+++	—	—	+	Weakness of legs +; palpitation on movement +
24	One finger right of left sternal margin	One finger inside of nipple line	+	++	+	—	—	Legs +	Brachial sound +; numbness of legs and fingers +
25	Normal.....	Normal.....	+	Murmur ++	+	—	—	Legs +	Brachial sound +; tenderness of calf muscles +; palpitation on movement +
26	Right sternal margin	One finger outside of nipple line	++	++	+++	—	—	+	Numbness of legs
27	Midline.....	Just inside of nipple line	+++	Murmur +++	+	—	—	+	Brachial sound +; tenderness of calf muscles +; liver palpable two fingers under the rib arch
28	Midline.....	Nipple line.....	+	+++	+	—	—	+	Brachial sound +; numbness of legs and fingers +; Chaddock +
29	Right sternal margin	Nipple line.....	++	+++	+	Very weak	—	+	Brachial sound +; tenderness of calf muscles +
30	Right sternal margin	Nipple line.....	++	+++	—	—	—	++	Brachial sound weak +; weakness of legs +; tenderness of calf muscles +; Chaddock +
31	Right sternal margin	Nipple line.....	—	Murmur ++	++	—	—	Legs +	Brachial sound very weak +; numbness of legs +; tenderness of calf muscles +
32	Normal.....	Normal.....	+	+++	+	Active	Weak	+	Brachial sound +; numbness of finger-tips and legs +; tenderness of calf muscles +
33	Midline.....	Nipple line.....	+++	++	—	Right normal, left —	Right normal, left —	—	Brachial sound +
34	Midline.....	Nipple line.....	++	++	++	Normal	Weak	++	Brachial sound +; weakness of legs +; liver palpable two fingers under the rib arch; Chaddock +
35	Right sternal margin	Nipple line.....	++	+++	++	—	—	—	Brachial sound +; tenderness of calf muscles +; Chaddock +; liver palpable two fingers under the rib arch
36	Midline.....	Nipple line.....	++	+++	+	Active	Active	Legs +	Brachial sound +; numbness of legs +
37	Midline.....	One finger inside of nipple line	++	+++	+++	—	—	+	Brachial murmur +; numbness of fingers and legs +; tenderness of calf muscles +; Chaddock +
38	Right sternal margin	Nipple line.....	++	+++	+++	—	—	+	Palpitation on movement +; Chaddock +
39	Right sternal margin	Just inside of nipple line	+++	++	+++	Weak	—	+	Brachial sound +; tenderness of calf muscles +; weakness of legs +; palpitation on movement +
40	Midline.....	Nipple line.....	++	+++	++	Normal	Weak	+	Brachial sound +; tenderness of calf muscles +; weakness of legs +; urine: protein, trace; indican +
41	Right sternal margin	Just inside of nipple line	++	+++	+	Very active	Active	+	Brachial murmur +; Chaddock +; weakness of legs +
42	Right sternal margin	Nipple line.....	+++	+++	+	Very active	Active	Legs +	Brachial sound +; urine: protein, trace
43	Midline.....	Nipple line.....	++	+++	+	Active	Active	+	Brachial murmur +; weakness of legs +; urine: protein, trace
44	Normal.....	Nipple line.....	++	+++	+	Weak	Weak	+	Brachial murmur +; numbness of fingers and legs +; urine: protein, trace
45	Normal.....	Normal.....	+	+++	—	Very weak	Very weak	+	Brachial murmur +; numbness of finger-tips and legs +
46	Midline.....	Just outside of nipple line	++	++	+	Very weak	—	+	Brachial sound +; urine: protein, trace
47	Midline.....	Nipple line.....	++	++	+	—	—	+	Brachial sound +; numbness of legs +

readily proved by pressing the skin, but in which there is increase in body weight, which decreases with diuresis) was often proved to exist by means of diuretics.

Nervous System: In general disturbances of motility, sensibility, etc., prevail, especially at the under part of the body. Hypesthesia and paresthesia are the common feature in beriberi. Weakness of the under limbs, which sometimes grows to a real paralysis, is often observed; the patients walk as if they walk in a muddy marsh. The knee jerks and Achilles reflexes are often absent, but in some cases, especially at the beginning of this disease, there are increased and very active tendon reflexes. The skin reflexes also are often absent or weak. Tenderness and hardness (Chaddock) of the muscles of the under limbs, especially of the calf muscles, are often observed. Abnormal softness of the calf muscles is not the common feature. In none of our cases was the contracture of the ankle joints in consequence of the peroneal paralysis marked. Hypesthesia and paresthesia also were proved to exist at the upper limbs and around the mouth. Edema and paresis of the glottis was sometimes recognized by the hoarseness of the voice.

Respiratory Quotient: The respiratory quotient ranged from 0.67 to 0.98, the average being 0.82, which coincides with the value of normal subjects.

Basal Metabolism: Comparing the basal heat production predicted by means of the Harris and Benedict formula with that actually measured, we have found that 87.3 per cent of cases and 80.4 per cent of measured times show deviations less than $\pm$ 15 per cent from the standards, and 86.2 per cent of cases and 74.7 per cent of measured times are within $\pm$ 10 per cent. A comparison of the heat production per square meter of body surface per hour with the Aub and Du Bois standards shows 92.5 per cent of cases and 88.5 per cent of measured times to be within $\pm$ 15 per cent, and 86.2 per cent of cases and 71.2 per cent of measured times to be within $\pm$ 10 per cent of the standards. Nine fresh cases in which treatment had not been given showed normal basal metabolism, except one with a somewhat high value. The cases with a basal metabolism higher than + 15 per cent of the standards have always shown a pulse rate of more than 80, i. e., the involvement of the cardiovascular system has always been significant. Case 21 showed on the first and third days a very high basal metabolism and high pulse rate, while on the second day there was an almost normal basal metabolism with quiet pulse. Case 26 also showed on the first day a very high basal metabolism and high pulse rate, on the succeeding days a normal basal metabolism with lower pulse rate. We are not ready to explain the very low metabolism in cases 5 and 9. It is not certain whether this occurred as the result of this disease or because of some unknown reason as we sometimes find this condition in normal subjects.

The clinical symptoms in these cases are not sufficient to explain this low metabolism. On the other hand, we have seen some cases that assumed a marked diminution of the basal metabolism in the course of this disease. These patients are apt usually to show distinct paralysis, especially of the under limbs, and atrophy of the muscles. Table 3 gives examples of such cases.

The report of the cases in table 3 follows:

TABLE 3.—*Cases in Which Paralysis Developed in the Course of the Disease*

Case	Date	Height in Cm.	Weight in Kg.	Surface Area (Du Bois Height-Weight Formula) Square Meters	Pulse Rate	Respiration Rate	Calories for Each 24 Hours	Calories per Square Meter per Hour (Du Bois)	Basal Metabolic Rate: Du Bois Standards, per Cent	Basal Metabolic Rate: Harris and Benedict Standards, per Cent	Body Temperature, C.
1	5/29	156.6	38.9	1.35	88	19	1,675	51.7	+12.4	+30.4	37.8
	6/17	.....	44.9	1.41	84	13	1,408	41.6	— 9.5	+ 3.0	36.7
	6/29	.....	40.5	1.36	82	20	1,211	37.1	—19.3	— 7.3	36.2
	7/10	.....	42.7	1.38	95	19	1,275	38.5	—16.3	— 4.5	36.4
	7/14	.....	43.6	1.39	62	18	1,201	36.0	—21.7	—10.9	....
	7/17	.....	39.0	1.35	56	17	1,175	36.8	—20.0	— 8.6	36.7
	7/29	.....	37.5	1.31	66	23	1,056	33.6	—27.0	—16.4	36.5
	8/ 5	.....	37.6	1.31	68	19	1,160	36.9	—20.0	— 8.4	36.5
2	7/27	162.5	51.5	1.54	75	21	1,408	38.1	— 7.1	— 3.1	36.5
	7/29	.....	51.8	1.54	72	16	1,353	36.6	—10.8	— 7.1	36.6
	8/22	.....	47.4	1.48	62	14	1,016	28.6	—30.2	—27.2	36.4
	8/29	.....	48.1	1.49	66	21	1,100	31.0	—21.5	—21.7	36.4

Patient 1 was 14 years and 5 months of age; patient 2, 19 years and 6 months.

In case 1 the vitamin B medication given consisted of intravenous injection of extract of rice bran (oryzanin), June 20, 10 cc.; July 1, 10 cc.; July 13, 10 cc.; July 14, 10 cc.; July 15, 5 cc., and July 16, 5 cc. From July 23 extract of rice bran, 10 Gm. per day, was given regularly until the patient left the hospital.

In case 2, the vitamin B medication consisted of 40 Gm. of spelzon (a Japanese vitamin B proprietary preparation), July 9; 26 Gm. of spelzon, July 10, and 3 Gm. of extract of rice bran (oryzanin) July 11. From July 12, 10 Gm. of extract of rice bran per day was given regularly until the patient left the hospital.

REPORT OF CASES

CASE 1.—J. S., a houseboy, aged 14 years and 5 months, was admitted to the hospital, May 25, 1922, complaining of dyspnea, oppression in the chest and some fever (from otitis media).

There was nothing special in the family history. He had had measles when 6; had been twice vaccinated. He had had severe stomach and intestinal disease when 3. Since then he had always been somewhat weak, but had had no particular disease. He had had severe beriberi of the cardiovascular type when 13.

Since the beginning of this month he complained of heaviness of the legs and palpitation which became severer on movement. He was somewhat constipated; the appetite was unchanged. The evening of May 19 about 9 he suddenly became pale and complained of nausea and tension of the abdomen, but no pain. A physician diagnosed the case as beriberi. The patient stayed in bed, but dyspnea and the oppression in the chest continued. Now and then pain was felt at the cardial region and the left hypochondrium. The face was swollen but there was no edema at the tibial edge. Since then he had had hypesthesia of the legs, fingertips, at the circumference of the umbilicus, and in the lips. Motility was quite normal. The voice had become somewhat hoarse.

Examination showed the pupillary reflexes normal. The teeth and tonsils were in good condition. The lungs were intact. There was no enlargement of the heart; the second pulmonic sound was divided and somewhat accentuated; the second aortic sound was divided and the systolic murmur was audible. Crural and brachial sounds were recognized. There was tenderness of the abdomen under the umbilicus. The liver was not palpable. The upper limbs were

intact with normal tendon reflexes. The knee jerks and Achilles reflexes were negative. Weakness of the legs was present but no paralysis. Urinalyses showed indican positive, no protein and no casts.

The heart was enlarged in the course of observation; June 20, the area of absolute dulness reached to the right sternal margin, to the upper edge of the third rib and the left nipple line; the area of relative dulness was a half finger to the right side of the right sternal margin, to the upper edge of the second rib and the left nipple line. The walk had become awkward and paralysis of the peroneal nerve was evident at this time. It was especially marked from June 26 to July 20, after which it became better. By August 5 the walk had become nearly normal. From June 19 to 29 the patient took somewhat less nourishment but the weight of the body was higher at this time (owing to the edema); at other times he always took an adequate amount of food to maintain vigor. The blood pressure on admittance was 100 systolic, 30 diastolic, and June 20, 120 systolic, 45 diastolic. Many times from June 20 and regularly after July 23 a large amount of vitamin B medication was tried. The basal metabolism was consistently low from June 29 to August 5.

CASE 2.—K. K., a stationer's attendant, aged 19 years and 6 months, was admitted to the hospital, July 23, 1922, complaining of weakness, palpitation on movement and pulsation at the epigastrium, oppression in chest, dyspnea and edema.

He had had measles when a child; was twice vaccinated. Since the end of June he had suffered weakness and edema of the legs; since about the tenth of July, palpitation on movement and pulsation at the epigastrium.

Examination showed the pupillary reflexes normal. The lungs were intact. The area of absolute cardiac dulness was from the midline to the upper edge of the fourth rib and two fingers inside the nipple line; the area of relative dulness from the right sternal margin to the upper edge of the third rib and one finger inside the nipple line. The second pulmonic sound was somewhat accentuated. The crural sound was clappering, the brachial sound audible. The knee jerks and Achilles reflexes were negative; there was tenderness of the calf muscles; the walk was normal. The blood pressure was 134 systolic and under 40 diastolic.

Beginning August 9, a large amount of vitamin B medication was tried; still by the end of August the paralysis of the under limbs, especially of the peroneal nerve, had become noteworthy. This was accompanied by hypesthesia of the legs and the circumference of the umbilicus. The food intake was normal. The basal metabolism at the end of July was normal and at the end of August distinctly low.

These two cases showed distinct diminution in the basal metabolism during the course of the disease. The marked feature appearing parallel with this diminution was the paralysis of the under limbs. We have also found such diminution in the basal metabolism in other diseases with paralysis or atrophy.

SUMMARY

1. In most cases of beriberi quite normal values in the basal metabolism and respiratory quotient were found.

2. When cardial incompetence threatened an increased basal metabolism was observed.

3. When paralysis and atrophy became remarkable a diminution in the basal metabolism occurred.

THE USE OF INSULIN BY MOUTH*

H. R. MILLER, M.D.
NEW YORK

The parenteral use of insulin has obvious disadvantages; consequently, a method for the oral use of insulin would be valuable. The authors cited below show how frequently this attempt has been made and with what unsatisfactory results.

Harrison [1] tried to administer insulin in alcoholic solution. He gave, by mouth, from 20 to 40 units of insulin, and seems to have obtained a fall in blood sugar in an occasional case. Similarly, Winter [2] administered insulin in a 20 per cent alcoholic solution by mouth (stomach tube) to rabbits. He, too, observed a drop of the blood sugar in some instances (rabbits, also in man).

Sansum, Blatherwick and others [3] concluded, after repeated trials of administration by mouth, that insulin was efficient by the hypodermic route only. Orally they gave as much as twenty-five times the subcutaneous dose to patients and to experimental animals. Murlin, Sutter, Allen and Piper [4] gave large amounts of slightly acidified insulin extract. Their hope was that some of this material would fortuitously leave the stomach and thus reach the circulation before gastro-intestinal enzymes would affect the insulin. An insulin precipitate with protein was also tried. Furthermore, they administered insulin in alcoholic solution to normal rabbits and to partially depancreatized dogs. Their results for animals and human beings were not constant and, therefore, unsatisfactory. Salen [5] confirmed this opinion. Finally, Sansum and his co-workers made use of capsules and tablets coated with phenyl salicylate. Capsules containing insulin preparations were dipped in phenyl salicylate and enclosed in larger gelatin capsules. Further trial of this method was urged as offering a possibility for a practical means of giving insulin by mouth. They stressed the value of putting within the capsule, together with the insulin preparation, some substance that would help to delay the destructive action of trypsin. Torrey [6] obtained a

---

* From the medical service at the New York Post-Graduate Hospital.

1. Harrison, G. A.: Brit. M. J. **2**:1204 (Dec. 22) 1923.
2. Winter, L. B.: J. Physiol. **58**:18 (Oct.) 1923.
3. Sansum, W. D.: Blatherwick, N. R.: Smith, Florence H.; Long, M. Louisa; Maxwell, L. C.; Hill, Elsie; McCarty, Ray; and Cryst, J. H.: J. Metab. Research **2**:641 (May-June) 1923.
4. Murlin, J. R.; Sutter, C. C.; Allen, R. S., and Piper, H. A.: Endocrinology **8**:331 (May) 1924.
5. Salen, Ernst: Acta med. Scandinav. **60**:1, 1924.
6. Torrey, E. W.: Am. J. Electroth. & Radiol. **41**:319 (Oct.) 1923.

rather striking depression of the blood sugar level in diabetic patients from the oral use of pigs' pancreas extracts (fresh). He experimented with four different kinds of extracts and described the process of preparation of each. Rather indifferent results were published by Mendel, Wittgenstein and Wolffenstein [7] with a dry insulin preparation given by mouth.

The student of the subject is impressed with the vagaries of the effects from the oral use of insulin. Apparently, at times, there is a flicker of hope that insulin by mouth is effective, as evidenced in a marked lowering of the blood sugar level; but it is well to remember in this connection that the diabetic patient, as a rule, is being starved during the experiment, and that during starvation the blood sugar may fall remarkably of its own accord. Mosenthal [8] has shown this. One of his diabetic patients had a fall of 80 mg. in blood sugar from 9 a. m. to 5 p. m. (started at 220 mg. and fell to 140 mg.); in another patient the blood sugar decreased from 315 mg. at 9 a. m. to 263 mg. at 5 p. m. (a fall of 52 mg.). Spontaneous descent of the blood sugar level in the diabetic patient, accordingly, may be responsible for a share of the fall in blood sugar noted in all experiments cited above. With this in mind our patients tested received no food before or after the use of insulin by mouth, in order to prevent confusion from a possible postprandial hyperglycemia as a complicating factor. It is, of course, important to know whether the preparation taken by mouth is absorbed from the stomach or intestines and particularly whether this is necessary when some form of capsule method is used. The roentgen ray would prove valuable in ascertaining the course and fate of opaque capsules.

We attempted to give the usual stock Lilly preparation of insulin in 95 per cent alcohol solution or absolute alcohol by mouth. Our method was to use not more than 3 minims of insulin, regardless of the strength, in not less than 1 cc. of alcohol (either absolute or 95 per cent solution) placed in the ordinary gelatin capsule, which was then dipped in keratin solution. The keratin solution was a 7 per cent glacial acetic acid preparation. We discovered early that if the alcoholic concentration was reduced to less than 75 or 80 per cent, osmosis took place through the gelatin capsule wall. This may explain the failure of those investigators who gave insulin in alcoholic solutions of low strength.

Patients received their usual diet the day before insulin was administered by mouth but fasted after supper, throughout that night, and the next day until the end of the experiment. Blood was taken for a blood sugar reading, then insulin by mouth administered immediately, and no food given until the termination of the experiment. A group of nine

7. Mendel, B.; Wittgenstein, A., and Wolffenstein, E.: Klin. Wchnschr. **3**: 470 (March 18) 1924.

8. Mosenthal, H. O.: Tice's Practice of Medicine, p. 69.

nondiabetic patients received insulin by mouth under these precautions and by this method. Table 1 illustrates the failure of these nondiabetic patients to show any appreciable drop in blood sugar.

It is difficult to understand why, if insulin by mouth has any effect at all, it failed to influence the blood sugar of these nondiabetic patients. We are therefore compelled to believe that insulin by mouth—certainly in nondiabetic patients—is not absorbed into the general circulation at

TABLE 1.—*Absence of Any Appreciable Effect on the Blood Sugar of Nondiabetic Patients from the Use of Insulin in Strong Alcoholic Solutions Administered by Mouth*

Case	Fasting Blood Sugar	Insulin by Mouth	Continued Fast	Final Blood Sugar	Change in Blood Sugar
1	138 mg.	64 units	2 hours 35 minutes	108 mg.	—30
			5 hours 30 minutes	116 mg.	—12
2	93 mg.	40 units	4 hours	94 mg.	+ 1
3	92 mg.	96 units	7 hours	89 mg.	— 7
4	88 mg.	48 units	5 hours	85 mg.	— 3
5	84 mg.	48 units	5 hours	77 mg.	— 7
6	86 mg.	96 units	8 hours 30 minutes	99 mg.	+13
7	63 mg.	40 units	4 hours	65 mg.	+ 2
8	57 mg.	40 units	4 hours	78 mg.	+21
9	83 mg.	48 units	4 hours 25 minutes	96 mg.	+13

TABLE 2.—*Influence of Insulin in Strong Alcoholic Solution Given by Mouth, on the Blood Sugar Level of Diabetic Patients*

Case	Sex*	Age, Years	Fasting Blood Sugar	Units of Insulin	Continued Fast	Drop of Blood Sugar to	Change in Blood Sugar, Mg.	Fasting Blood Sugar	Units of Insulin by Mouth, Units	Continued Fast	Drop of Blood Sugar to	Change in Blood Sugar, Mg.
1	♂	68	167	0	6 hours	143	—24	230	64	7 hours 55 min.	153	—77
2	♀	51	188	0	6 hours	176	—12	172	96†	7 hours	144	—28
								356	264†	8 hours	214	—142
3	♂	38	232	0	7 hours	208	—24	248	96	7 hours	156	—92
4	♀	58	168	0	4 hours 5 minutes	150	—18	174	64	5 hours	125	—49
5	♀	54	128	0	6 hours	111	—17	166	48	7 hours	103	—63
								137	96	2 hours	50	—87
6	♀	49	143	0	4 hours 5 minutes	118	—25	167	64	6 hours	141	—26
7	♂	36	...	...	.....	...	....	204	64	5 hours	150	—54
8	♀	52	...	...	.....	...	....	231	96	7 hours	158	—73
9	♀	42	...	...	.....	...	....	283	96	7 hours	202	—81

* In this table, ♂ indicates male; ♀, female.
† For these large doses highly concentrated preparations of insulin were employed in order to keep the total amount of alcohol as low as possible.

all, or at most in insufficient quantity. In any case, even if absorbed it does not affect the blood sugar level.

Table 2 demonstrates the effects of insulin given by mouth, in the same manner, to diabetic patients. The blood sugar level nearly always fell after such use of insulin and in some instances at least this decline was much greater than we would expect starvation alone to accomplish. Most of the patients listed were put through a "control day" to note the effect of starvation alone on blood sugar. In six such diabetic patients,

starved only, the average drop in blood sugar was 20 mg. over a period of from four to seven hours This is contrasted with the results in diabetic patients, the same six (plus three others), who received insulin by mouth while starving and in whom the average blood sugar drop was 68 mg. over an interval of time that ranged from two to eight hours.

An important consideration is the height of the blood sugar level at the commencement of the experiment. For instance, the fasting blood sugar of case 5, table 2 (chart 1), could not be expected to show as marked a decline either from starvation alone or from starvation plus insulin by mouth, as in case 2 (chart 2) in which the fasting blood sugar, on one of the days of the experiment, was 356 mg. Yet despite all

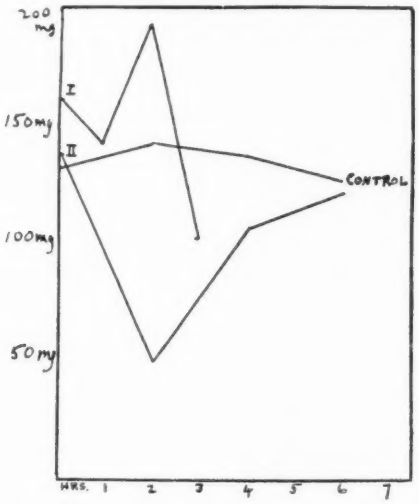


Chart 1.—Blood sugar curves of diabetic patient 5. The control test (starvation only) was made Dec. 18, 1925, while 48 units of insulin in 95 per cent alcohol solution was given by mouth, Nov. 28, 1925, and 96 units, under similar conditions, Dec. 21, 1925. The records in detail are:

48 Units of Insulin (I)	96 Units of Insulin (II)	Control—No Insulin
A. M. 8:40 Blood sugar (fasting)... 166 mg.	A. M. 8:30 Blood sugar (fasting)... 137 mg.	A. M. 8:30 Blood sugar (fasting)... 128 mg.
8:45 Insulin by mouth	8:35 Insulin by mouth	
9:40 Blood sugar 142 mg.	10:30 Blood sugar 50 mg.	10:30 Blood sugar 143 mg.
10:40 Blood sugar 182 mg.	12:30 Blood sugar 119 mg.	12:30 Blood sugar 136 mg.
11:40 Blood sugar 103 mg.	P. M. 2:30 Blood sugar 121 mg.	P. M. 2:30 Blood sugar 126 mg.

critical inferences, one may indicate that the use of insulin by mouth, as administered by the method outlined above, seemingly lowered the blood sugar level in diabetic patients. Unfortunately, we could carry out no roentgen-ray studies to determine the fate of the keratin coated capsules in the gastro-intestinal tract. The examination of the stools for their recovery was not always satisfactory.

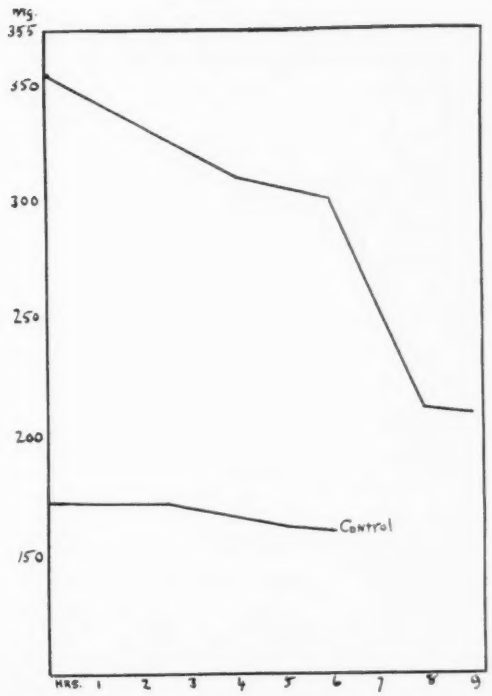


Chart 2.—Two blood sugar curves in diabetic patient 2. The control test (starvation only) was performed, Dec. 22, 1925, while 264 units of insulin in 95 per cent alcohol solution was given by mouth, Jan. 6, 1926.

264 Units of Insulin			Control—No Insulin		
A. M.	8:00	Blood sugar (fasting)..... 356 mg.	A. M.	8:30	Blood sugar (fasting)..... 188 mg.
	8:05	Insulin by mouth			
	10:00	Blood sugar..... 336 mg.		10:30	Blood sugar (fasting)..... 188 mg.
	12:00	Blood sugar..... 314 mg.		12:30	Blood sugar (fasting)..... 178 mg.
P. M.	2:00	Blood sugar..... 302 mg.	P. M.	2:30	Blood sugar (fasting)..... 176 mg.
	4:00	Blood sugar..... 214 mg.			

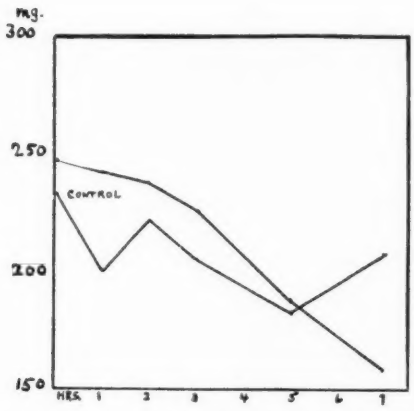


Chart 3.—Comparison of the fall in blood sugar in diabetic patient 3. The control test (starvation only) was carried out, Dec. 28, 1925, and the experiment of giving by mouth 96 units of insulin in 95 per cent alcohol solution, under similar conditions, was performed, Dec. 29, 1925. The records in detail are as follows:

96 Units of Insulin		Control—No Insulin	
A. M.	8:30 Blood sugar (fasting)..... 248 mg.	A. M.	8:30 Blood sugar (fasting)..... 232 mg.
	8:35 Insulin by mouth		
	9:30 Blood sugar..... 242 mg.		9:30 Blood sugar (fasting)..... 204 mg.
	10:30 Blood sugar..... 238 mg.		10:30 Blood sugar (fasting)..... 234 mg.
	11:30 Blood sugar..... 225 mg.		11:30 Blood sugar (fasting)..... 205 mg.
P. M.	1:30 Blood sugar..... 188 mg.	P. M.	1:30 Blood sugar (fasting)..... 184 mg.
	3:30 Blood sugar..... 156 mg.		3:30 Blood sugar (fasting)..... 208 mg.

CONCLUSIONS

We are not in a position as yet to offer this method of insulin administration for the treatment and control of diabetic patients. It appears likely, however, that insulin given in absolute alcohol or 95 per cent alcohol solution (total solution not to be below 85 per cent alcohol), within keratinized capsules, lowers the blood sugar level of diabetic patients. As already suggested, we should prefer to learn the fate of these keratin coated capsules after they are swallowed in order to ascertain the amount of insulin which may enter the circulation and to gage such factors as absorption and dangers. We report our results, at this time, however, so that carefully controlled experiments may be assembled on a larger scale and thus lead to a definite evaluation of any merit this method may possess.

THE GROWTH OF THE LONG BONES IN CHILDHOOD

WITH SPECIAL REFERENCE TO CERTAIN BONY STRIATIONS OF THE METAPHYSIS AND TO THE RÔLE OF THE VITAMINS *

H. A. HARRIS, M.B.

ST. LOUIS

INTRODUCTION

The mainspring of medical research is the interpretation of the phenomena of disease in terms of disordered physiology. The widest gap in the search for this interpretation is seen in diseases of the bony, muscular and blood vascular systems. The innumerable systems of classifying diseases of bone, teeth, muscle and blood vessels indicate that either the clinical and pathologic data or the normal developmental processes have not been elucidated. Our knowledge of the anatomy and physiology of bone is limited. On the one hand, little is known of the nerve supply and lymphatic supply of this tissue. Attempts to interpret the function of the periosteum have produced a series of conflicting views from Hunter [1] and Duhamel,[2] Cheselden and Haller, Ranvier and Sharpey to Tillier, Macewen [3] and Gallie and Robertson.[4] The origin of the osteoblast is still undecided, though recent workers such as Stump [5] and Fell [6] tend to regard the chondroblast, osteoblast and osteoclast as closely related descendants of the primitive connective tissue cell. The experimental work in rickets has lead to a number of "schools" in which the calcium, phosphorus, vitamin A and vitamin X have been successively brought into the limelight. The purely graphostatical laws of the structure of the bony lamellae presented by Meyer [7] and Wolff [8] have been shown by Jansen [9] to be

* From the Institute of Anatomy, University College, London, and Washington University Medical School.

1. Hunter, John: The Works of John Hunter, London, 1835, vol. 4, p. 317.
2. Duhamel: Sur le developpment et la crue des os, Mém. Acad. d. Sc., 1742, p. 497, and 1743, p. 187.
3. Macewen, W.: The Growth of Bone: Observations on Osteogenesis, Glasgow, 1912.
4. Gallie, W. E., and Robertson, D. E.: The Repair of Bone, Brit. J. Surg. **7**:211 (Oct.) 1919.
5. Stump. W. C.: The Histogenesis of Bone, J. Anat. **59**:136-154, 1925.
6. Fell, H. B.: The Histogenesis of Cartilage and Bone in the Long Bones of the Embryonic Fowl, J. Morphol. & Physiol. **40**:417-460, 1925.
7. Meyer, H.: Die Architectur der Spongiosa, Reichert and Dubois, Raymond's Arch. f. Anat., 1867.
8. Wolff, Julius: The Law of the Transformation of Bones, 1892.
9. Jansen, Mark: On Bone Formation, Leiden, 1920.

inadequate. The relationship of the size of the medullary cavity to the size and character of the contained bone marrow is still a mystery, although this involves the two tissues, bone and marrow, which are characterized by the maximum power of physiologic growth, repair and rapid hypertrophy in the human economy. Similarly, the muscular system, forming 43 per cent by weight of the healthy adult, is subject to a group of diseases in which no correlation has, as yet, been found between the normal physiologic and the varied pathologic processes.

First, it is proposed to describe in detail a case that illustrates the actual process of bone growth in the long bones of a child over a period of two years, with the registration of the effects of severe illness thereon. Secondly, the whole problem of the genesis of bony striations in the metaphyseal region of the long bones will be discussed.

PART I

AN ILLUSTRATIVE CASE

A girl, aged 2 years and 8 months, was admitted to the hospital with measles and severe bronchopneumonia. There was a history of bronchopneumonia at 16 months and of marked liability to colds. Evidence of consolidation of the lung persisted for nine weeks and there was marked bronchiolectasis with clubbing of the fingers; spasmus nutans developed and persisted for three weeks. There was no history or evidence of rickets; the child was discharged with a persistent cough and a slight evening temperature, and was supervised by the social workers as a possible case of tuberculosis. The child was well nourished and more than the average weight, but suffered a great deal from cough. The home conditions were such that the child spent a considerable portion of her time indoors. Eight months later, the child was readmitted with whooping cough and severe bronchopneumonia, temperature 105, pulse 160 and respirations 80 per minute. The signs were most marked over the left lung and the right base. After a stay of five weeks in the hospital, she was discharged in much the same condition as formerly, but the decreased movement of the left side of the chest was more marked and there was a difference of 1 inch (2.5 cm.) in the measurement of the left and right semiperimeter of the chest. The cough was paroxysmal and the sputum copious.

One year later, the child was admitted with a severe bronchopneumonia, palpable spleen, clubbed fingers, temperature 104.5, pulse 150 and respirations 60. The cardiac area was definitely enlarged as regards visible pulsation; the heart was enlarged to percussion, and Traube's space was diminished by the splenic enlargement. The skin over the chest was somewhat transparent, the nails were brittle, the clubbing of the fingers was marked. On discharge the child presented the picture of bronchiolectasis with moderate emphysema. No laboratory evidence of the presence of tuberculosis was obtained at any time, the Wassermann reaction was negative, nor was there any sign of rickets. Thus, in three successive years the patient had been subjected to three distinct illnesses: (1) measles with bronchopneuomonia, (2) whooping cough with bronchopneumonia and (3) bronchopneumonia.

A routine roentgenogram of the chest and epiphyses of the child while attending the outpatient clinic after the second illness showed the presence of certain lines of dense bone near the end of the diaphyses. These lines of dense bone were most marked in the lower limb, were clearly seen at the shoulder and wrist, and were least obvious at the elbow. Accordingly, as no reference to the existence of these lines apart from rickets had been seen, roentgenographic examination was made of the long bones of the child at successive dates over a period of two

years. One of the roentgenograms taken after the second illness shows a line of dense bone as a transverse striation in the diaphysis about 1 cm. away from the epiphyseal line of the lower end of the femur, upper end of the tibia and lower end of the tibia. There is another dense striation much nearer the epiphyseal line, in close proximity to the metaphysis. These two lines were regarded as being formed during the first and second periods of acute illness. At the lower end of the tibia there were faint traces of transverse striations more proximally placed in the diaphysis and these were regarded as the residue of the attack of bronchopneu-

Fig. 1.—Leg bones showing transverse bony striations.

monia which the child suffered at 16 months, and of the "severe colds" in babyhood, which were probably accompanied by some bronchopneumonia.

After three roentgenograms had been taken over a period of thirty-one weeks, the patient had another severe attack of bronchopneumonia and a roentgenogram was taken during the convalescence period seven weeks after the onset of the attack. The roentgenogram, figure 1, showed a third series of lines of dense bone formed near the metaphysis almost at the ends of the diaphyses.

Roentgenograms were taken over a period of two years and the outlines of the roentgenograms were transferred to paper by pricking the outlines through a print on to a bristol-board and joining the pin pricks by a line. Figure 2 is a series of eight drawings from roentgenograms (marked *A* to *H*) taken over this period. The outlines of all eight roentgenograms were reduced to a uniform scale; the day, month and year are written below and the numbers 1, 2 and 3 indicate the transverse striations formed during the three successive acute illnesses.

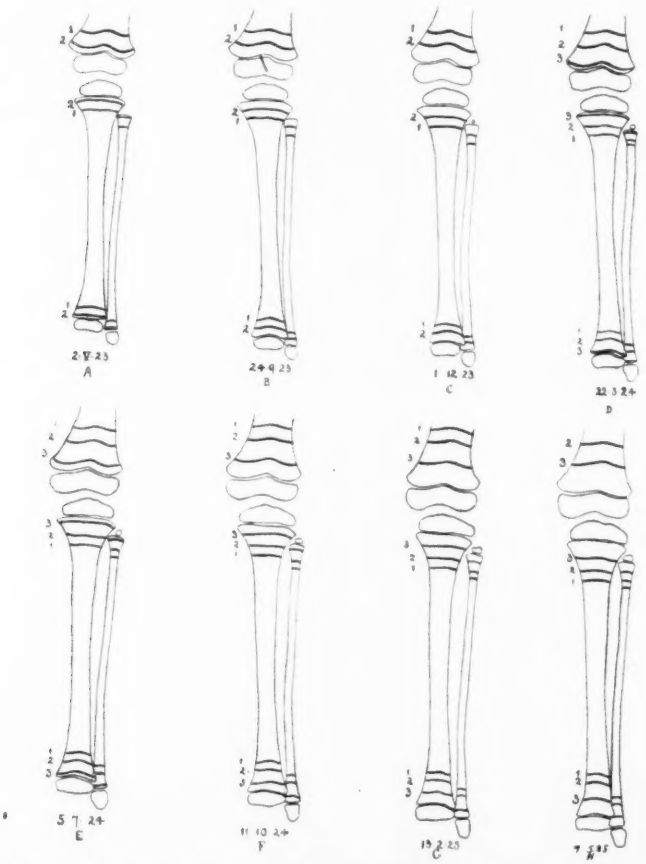


Fig. 2.—Outline of roentgenograms over a period of 106 weeks; the lines are numbered for the first, second and third periods of cessation of growth during the three acute illnesses.

Figure 3 was constructed from these roentgenograms, the abscissae representing the time in weeks of the various illnesses, the ordinates the length of the diaphysis, and the position of the transverse striations being numbered 1, 2 and 3. The dense lines show the superior and inferior limits of the diaphysis of the tibia and their gradual divergence gives the actual amount of growth at each end in centimeters and the gradient gives the rate of growth. The faint lines indicate

the transverse striations for the first two illnesses in the case of roentgenograms *A*, *B* and *C*, and for all three illnesses in the subsequent roentgenograms *D* to *H*.

Since the transverse striations remain steadfastly parallel and equidistant, we now have a convincing proof that there is no interstitial growth in the shaft of the tibia and all growth in length takes place by the apposition of new bone to the ends of the diaphysis at the metaphyses. Furthermore, the periods of slow growth from *A* to *B* and from *D* to *E* correspond to periods immediately following the illness, and these are followed by periods of rapid growth from *B* to *C*, and from *E* to *F* when the child was subjected to increased fresh air, sunlight and extra feeding during two successive autumns.

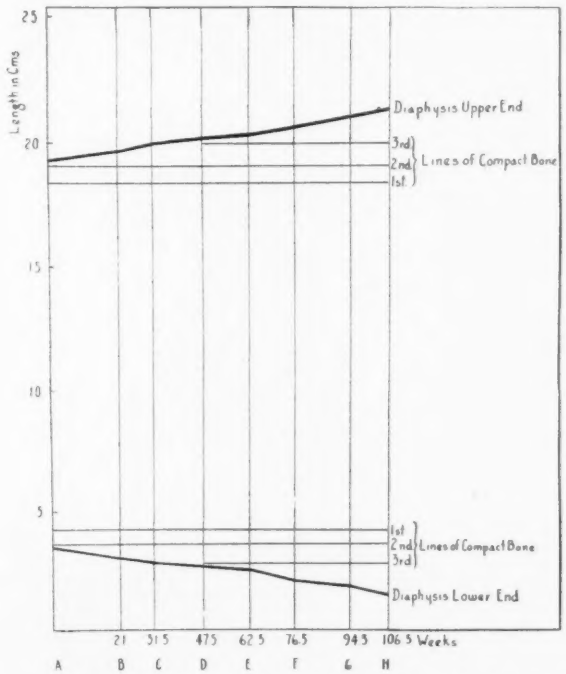


Fig. 3.—The growth in length of the tibia over a period of two years.

It can be seen from figure 2 that the distance between the lines at the lower end of the femur is different from that at the two ends of the tibia. Over a period of 106 weeks the total increase in length at the lower end of the femur is 2.1 cm., at the upper end of the tibia 1.9 cm., and at the lower end 1.8 cm. That is to say, the most active growth takes place at the lower end of the femur, and the growth at the upper end of the tibia has been slightly in excess of that at the lower end of the tibia, in conformity with the accepted view that growth at the knee is a little more active than growth at the ankle and hip. The distances between the three lines at the lower end of the femur and at the two ends of the tibia also confirm this.

THE EXPERIMENTS OF HUNTER AND DUHAMEL

Hunter,[1] to ascertain whether the long bones are elongated by the interposition of new bone in the interstices of the old, performed the following experiment: He bored two holes in the tibia of a young pig, one near the upper end, and the other near the lower; the space between the holes was exactly 2 inches (5 cm.). A small lead shot was

Fig. 4.—Multiple transverse striations in the shaft of the tibia of a girl, aged 14 years.

inserted into each hole. When the bone had increased in length by the growth of the animal, the pig was killed and the space between the two shots was still found to be exactly 2 inches.

In the Palmer edition of the works of John Hunter there is an erroneous account of the lead shot and silver stylet experiments of

Duhamel. This chapter in the history of bone growth is adequately discussed by Keith,[10] and as Keith says, "Duhamel has been unfortunate in his commentators." The experiments of Hunter and Duhamel in both pigs and birds show clearly that there is no intercalated growth in length in the diaphysis of the long bone. This fact is adequately confirmed by the observations over a period of two years on the tibia of our young patient. There is no justification for the statement of Macewen:[11] "Interstitial growth occurs in the diaphyses of long bones, contributing slightly to increase in length."

The lead shot experiment by Hunter on the tarsometatarsus of the fowl has been frequently adduced as evidence of interstitial growth. Keith[10] has shown both that Hunter probably understood the phenomenon of "drag on the periosteum" and that Humphrey described the phenomenon clearly in the explanation of the oblique course of the nutrient canal. In this respect it is interesting to note that the transverse striations tend to become less distinct toward the periphery, i. e., immediately beneath the periosteum. The "drag on the periosteum" accounts for the fact that the striations are more rapidly obliterated in close propinquity to the periphery of the bone. As Flourens[12] said, "Mais si, d'une part, des molécules nouvelles sont incessament déposées, si, d'autre part, des molécules anciennes sont incessament resorbées; il ya donc mutation continuelle de la matière."

PART II

BONY STRIATIONS IN THE METAPHYSIS

A. History.—The early roentgenograms of this patient were shown at a meeting of the Association of Anatomists in London in the summer of 1923 and, some time later, Professor Policard of Lyon called my attention to various reports in the French clinics of "stries osseuses dans le metaphysaire." Tillier[13] in 1920 described certain diametaphyseal lines in roentgenograms of the long bones of children, lines that were straight, very slightly sinuous, and of regular thickness. He used these lines as a justification for the view that the metaphysis had as individual an evolution as the diaphysis and the epiphysis and considered in detail the particular pathologic conditions found. After examination of cases of rickets, tuberculosis, osteomyelitis and synosteosis of the inferior extremities of the tibia and fibula, Tillier concludes that the line of dense bone represents a region of accessory epiphyseal cartilage

10. Keith, Arthur: Menders of the Maimed, London, 1919, p. 212.

11. Macewen: Footnote 3, p. 198.

12. Flourens, M. J. F.: Recherches sur le developpement des os, Paris, 1842, p. 98.

13. Tillier, R.: Une particularité de Structure du Squelette Infantile Révélée par la Radiographie, Lyon Chir. **17**:433-488 (July-Aug.) 1920.

which later undergoes marked ossification and condensation and represents the union of primitive diaphysis with metaphysis. The frequency of juxta-epiphyseal fractures, especially at the inferior extremity of the radius and ulna, is attributed to bending strains in the region of these lines.

Mouchet [14] in 1921 described such lines in girls from 13 to 15 years of age who complained of vague pains in the lower limbs which were attributed to "growing pains." One of the girls presented three transverse striations at the inferior extremity of the right and left tibia and fibula. A single striation was seen at the lower end of the femur and at the upper end of the tibia but not at the upper end of the fibula. The cases described by Tillier were characterized by a single striation through the metaphysis, though he refers to a description by Broca of multiple lines in cases of rickets. Mouchet points out that the existence of three striations in the case of his girl patient negatives the view of Tillier, for three such lines could not, each and severally, indicate the union of two skeletal segments, the metaphysis and diaphysis. Also in Mouchet's case there was no history or evidence of rickets.

Bopp and Ulrich [15] in 1922 described two transverse striations in the inferior extremities of the bones of the left and right leg in a patient aged 46. The striations were situated at the line of the epiphyseal union and 1 cm. proximal. Faint lines also were seen at the upper extremity of the tibia and fibula, but there was no trace of these lines in the bones of the upper limb. These lines were not related to any traumatism, and no pathologic antecedents could be found; the Wassermann reaction was negative. Bopp and Ulrich incline to the view of Tillier that such lines represent a condensation in cartilage "rests" in the metaphysis.

In 1923 Hertz and Lévy-Lebhar [16] saw in the roentgenogram of the lower end of the tibia in a girl of 8 years seven lines, of which four were very distinct and the upper three less so. They point out the improbability of seven such parallel lines being accessory epiphyseal cartilages or of such lines marking two bony zones. One year later, in 1924, Dr. Mauclaire [17] presented a case with several striations in the long bones of a patient in whom there was no evidence of rickets. He discusses in detail the various views put forward and shows that none of the cases are adequately explained by either of the three theories put forward by previous investigators. Mauclaire points out that if addi-

14. Mouchet, A.: Stries transversales des metaphyses du femur, du tibia, et du perone, Bull. et mém. Soc. de chir. de Paris **47**:178-179, 1921.

15. Bopp and Ulrich: Stries metaphysaires chez un adulte de 46 ans, Bull. Soc. anat. de Paris **92**:676-677, 1922.

16. Hertz and Lévy-Lebhar: Sur les stries juxta-epiphysaires des os longs, Bull. Soc. anat. de Paris **93**:260-261, 1923.

17. Mauclaire: Stries osseuses transversales sur plusieurs os chez le méme sujet, Bull. Soc. anat. de Paris **94**:446-447, 1924.

tional strains were a factor in the etiology, one ought to find such striations in the os calcis, which is very susceptible to slight changes of use and disuse and registers the various forms of bony atrophy with facility and rapidity. The rachitic etiology is untenable as so many cases have been described in patients of various ages who present no history or evidence of rickets. These lines have not been reported in Madelung's disease, with marked rachitic changes at the distal extremity of the radius nor in cases of genu valgum.

B. The "Line Test" of Park and Howland.—In 1921 Park and Howland [18] described the "line test" for healing rickets. After treatment with cod liver oil, changes are detected by roentgenogram about the end of the third or fourth week, occasionally a little before. In the case of two children who died six days and twelve days after the beginning of cod liver oil medication there was no appreciable deposition of calcium salts on microscopic examination. The line gradually becomes thicker and thicker in cases of healing rickets and is more dense than other parts of bone. The pathologic studies of Schmorl have shown that in the process of healing the deposition of calcium salts takes place first in the cartilage on the epiphyseal side of the transitional zone, i. e., in the place where the lime salts would have been deposited had there been no rickets. The deposition in this locale is the cause of the linear shadow on the roentgenogram. Gradually, the material in the transitional zone is transformed into bone and becomes infiltrated with calcium salts. From two to three months are necessary for the completion of the process of repair and even then the trabeculae of the repaired zone show certain irregularities in the arrangement of the trabeculae.

In 1923 Evans [19] described certain cases of acute rickets in late childhood and adolescence, and he says, "The cartilage of conjugation may show a linear ossification bisecting the cartilage into two thinner disks. It is an early sign of recovery and is known as the line test."

C. Starvation in Rickets.—McCollum [20] and his co-workers observed healing of rickets in starvation. Ten rats with well developed rickets were starved to death over periods of time lasting from three to five days. In each case the line test of calcification was positive both on roentgenographic and histologic examination. The addition of 2 per

18. Park, E. A., and Howland, J.: The Radiographic Evidence of the Influence of Cod Liver Oil in Rickets, Bull. Johns Hopkins Hosp. **32**:341-344 (Nov.) 1921.

19. Evans, T. L.: Acute Rickets in Late Childhood and Adolescence, Brit. M. J. **2**:1212-1213, 1923.

20. McCollum, E. V.; Simmonds, S.; Shipley, P. G., and Park, E. A.: Studies on Experimental Rickets: XV. The Effect of Starvation on the Healing of Rickets, Bull. Johns Hopkins Hosp. **33**:31-33 (Jan.) 1922.

cent cod liver oil to the ricket producing diet also gave a positive line test in five days. McCollum suggested that starvation liberates from the tissues an organic factor or factors which cause calcium deposition to occur in the cartilage. This he ascribed to the increase of phosphorus in the blood. McCollum regards his experiments as "furnishing the first anatomical proof of the beneficial effect of starvation on the animal body. The good effects of fasting are given a new meaning, because the organism is able to adapt itself to pathogenic distortions of normal metabolic ratios when the burden of carrying on exogenous metabolism is removed. Since the starving body is capable of readjusting abnormal relations within itself it is easy to understand the benefit derived by a diabetic from occasional hunger days, and why it is that the wasted athreptic infant does not develop rickets."

McCollum as a protagonist of starvation is dismissing the fact that his so-called beneficial effect of starvation is really cessation of growth and heralds death. The athreptic child is too busy trying to hold on to life to grow, and not growing—develops no rickets. The fact that he develops no rickets may be equally well ascribed to the beneficial effect of athrepsy.

The recent spectacular assertions of de Bosanyi [21] to have cured rickets by hitherto undescribed antirachitic substances require careful examination from the point of view of cessation of growth. De Bosanyi asserts that he has cured rickets by the administration of hemoglobin, cystine, epinephrine and pilocarpine. Van Leersum previously said that he had cured rickets by hematoporphyrin. De Bosanyi treated rachitic rats by 5 per cent chlorophyl solution and showed healing of their rickets. He says, "But these animals, although they did not starve, lost a great deal of weight and died in two weeks." It is submitted that here again the bony striation which is regarded as that of healing rickets is really only a manifestation of cessation of growth and athrepsy.

D. Rickets in Relation to Cessation of Growth.—Pappenheimer [22] fed rats on a ricket producing diet:

> When, however, as exceptionally happens, no growth has occurred during the earlier weeks, the rachitic lesions are apt to be poorly developed. . . . We have also observed that rapid loss of weight, especially when associated with diarrhea, favors the deposition of calcium. This is comparable to the effect of complete starvation as described by McCollum, Simmonds, Shipley and Park.

---

21. De Bosanyi, Andor: Studies of Certain Hitherto Undescribed Antirachitic Substances, Bull. Johns Hopkins Hosp. **38**:72-74 (Jan.) 1926.

22. Pappenheimer, A. M.: Experimental Rickets in Rats: VI. The Anatomical Changes Which Accompany Healing of Experimental Rat Rickets Under the Influence of Cod Liver Oil or Its Active Derivatives, J. Exper. Med. **36**:336 (Sept.) 1922.

In the ribs of athreptic nonrachitic rats on a deficient dietary, or in which failure of growth had occurred because of infection, Pappenheimer found that the matrix of the zone of preparatory calcification was as densely calcified as in the normal bone. "In old animals, after the cessation of epiphyseal growth, or in larger animals, in which arrest of growth is artificially brought about by dietary deficiency, such as lack of fat soluble A, the trabeculae atrophy or become fused into a transverse plate of bone extending across the cartilage." It is submitted that this also is a bony striation indicating cessation of growth.

Hess, McCann and Pappenheimer,[23] feeding rats on a diet deficient in vitamin A, describe a thin continuous plate of fully calcified bone, limiting the cartilage and fusing with the calcified matrix. The skeletal changes in no way resemble those of rickets, and the authors state that "this is what might be expected in view of the stationary or declining weight and arrest of growth." Many of these rats had acute suppurative infections of the alimentary, respiratory and urogenital tracts. The skeletons of such rats showed no gross changes whatsoever.

E. The Transverse Striations in Scurvy.—Transverse striations in the shafts of the long bones have been described in scurvy by Lehndorff.[24] Dense bands of shadow, of variable width, have been described as "trümmerfeldzone," often several in number and crossing the shaft like "strips of embroidery." The "trümmerfeldzone" lies on the epiphyseal side of the metaphysis; on the diaphyseal side of the metaphysis a light zone has been described as "gerustmarkzone." These lines of increased earthy deposition and bands of decreased earthy deposition have been regarded as specific of scurvy. Such concentric lines of dense bone formation have also been described in the epiphyses and os calcis.

Tozer[25] has described the histologic findings in scurvy and has depicted the shortening of the rows of the cartilage cells and of the trabeculae. In figure 16 in her article describing a case of chronic scurvy, Tozer shows the typical transverse striation of condensed bone. The transverse striation is seen only in those cases of chronic scurvy which have presented cessation of growth over some period of time.

F. Fusion Lines.—The fusion lines between the epiphyses and diaphyses of the long bones have recently been described by Cope,[26] and

23. Hess, A. F.; McCann, G. P., and Pappenheimer, A. M.: Experimental Rickets in Rats: II. The Failure of Rats to Develop Rickets on a Diet Deficient in Vitamin A, J. Biol. Chem. **47**:395-409 (July) 1921.

24. Lehndorff, H.: Zur Kenntniss des Morbus Barlow, Arch. f. Kinderh. **38**: 161-167, 1904.

25. Tozer, F. M.: On the Histological Diagnosis of Experimental Scurvy, Biochem. J. **12**:445, 1918.

26. Cope, Z.: Fusion Lines of Bones, J. Anat. **55**:36-37, 1920-1921.

Stevenson,[27] in his exhaustive survey of ossification in the collection of human skeletal material in the Western Reserve Museum, has focused considerable attention on them. These lines of fusion appear in the nineteenth and twentieth years, and may persist to extreme old age both in the longitudinal section and in the roentgenogram of the bone. Such lines of fusion are either thin, slightly sinuous lines of extremely dense bone, or narrow belts of cancellous tissue of a greater degree of compactness than the surrounding bones. In the undersized person with a history of severe illnesses in childhood or adolescence the lines may be wide and compact and associated with premature fusion and cessation of growth before the nineteenth and twentieth years. Such lines are more easily distinguished at the knee, ankle and shoulder and are rarely seen at the elbow or wrist.

G. The General Distribution of Bony Striations.—Bony striations resembling those described in Part I of this article have been seen repeatedly in routine examination of patients and in particular they have been observed in those adolescents who have suffered severe exanthemas in late childhood. They have been observed in conjunction with those cases presenting the so-called "peribronchial" fibrosis to a marked degree in the lower lobes of the lung. The lines have been seen in the case of adult chronic invalids who have been in indifferent health after severe illnesses in childhood and are frequently associated with irregularities of dentition, both as regards eruption of the teeth, suppression of the third molar, and those irregularities of the palate associated with the adenoid facies. In one specimen of a femur of a 6 months fetus in the Anatomical Museum of University College there is a well marked line 1 cm. proximal to the epiphyseal line at the lower end of the femur.

Dr. McKim Marriott of St. Louis presented me with figure 4, the roentgenogram of the tibia of a girl, aged 14 years, who suffered great privation in Russia for thirteen years. At present the girl is dwarfed and shows no lesion except large tonsils. She was breast fed, did not walk or talk until 3 years of age, and her bones were then said to have been "soft." Figure 4 shows no trace of adolescent rickets, but nine lines of dense bone are seen at the lower extremity of the tibia within a distance of 5 cm. These lines do not pass to the circumference of the bone and are shorter and more attenuated as the distance from the epiphysis increases. The tibia presents only a slight degree of forward bowing in the shaft. The patient had been diagnosed as a "rickety dwarf."

A closely allied phenomenon is seen in deciduous trees. In the first place, the rings of wood laid down during the vernal ascent and

27. Stevenson, P. H.: Age Order of Epiphyseal Union in Man, Am. J. Phys. Anthropol. **7**:53, 1924.

autumnal descent of the sap have distinct structural characteristics. In addition to this seasonal variation, marked examples of cessation of growth can be seen. A deciduous tree subjected to an unsuitable environment, such as excessive drought, during the early summer responds by a premature formation of cork across the base of the leaf stem and one half of the foliage may be prematurely shed. This protective mechanism decreases the area of functional transpiration, and the deposit of cork at the base of the leaf stem presents that pathologic cessation of growth that is normally seasonal in the deciduous tree, and normally adolescent in the coniferous tree.

H. Rickets and the Vienna Report.—In a previous article [28] the clinical signs of early rickets employed by the Vienna School have been criticized. A few further remarks are necessary. The roentgenograms of the bones of a "normal" infant given by Wimberger [29] are not normal but show distinct bony striations at the upper and lower ends of the diaphysis of the tibia. These are evidence of periods of cessation of growth which may be due to any one or more of the causes that give rise to such lines. If on the various medical charts of the report the date of onset of an acute illness is marked it is obvious that the "line of dense ossification" may well be diagnosed as evidence of cessation of growth rather than as healing rickets. In charts 5 to 11, 14 to 17 and 19 and 21 an acute illness was present before healing rickets was diagnosed. In charts 22 to 27 there are several cases in which healing rickets was diagnosed roentgenographically by the line test within thirty days of acute influenza or bronchitis. A careful study of the medical charts and roentgenograms will show that bony striations occur quite distinct from the line of healing rickets. The roentgenograms are equivocal.

In a report of eighty-four selected cases examined histologically for evidence of rickets by Dalyell and Mackay, Wimberger [29] says that only twenty-eight were normal. Of the remainder, twenty-five showed rickets, three showed scurvy and twenty-eight showed syphilitic change, osteoporosis or other abnormal condition. Of the twenty-eight cases that were histologically diagnosed as rickets only ten were so diagnosed clinically before necropsy, and the two cases of proved scurvy, histologically diagnosed, were labelled as rickets before necropsy. This indicates that too much specificity cannot be credited to the "rickety rosary" and that every patient coming to necropsy, other than from sudden accidental death or acute poisoning in a healthy child, will tend to show abnormal features in the neighborhood of the epiphyses.

---

28. Harris, H. A.: Some Problems of Bone Growth, Proc. Roy. Soc. Med. (Sect. Electro-Therap.) **17**:35-48 (Oct.) 1924.

29. Wimberger, H.: A Study of Developing, Florid and Healing Rickets as Demonstrated by X-Ray Photography, Studies of Rickets in Vienna, 1919-1922, London, 1923, p. 204, plate I.

PART III

THE GENESIS OF THE TRANSVERSE STRIATIONS IN BONE IN RELATION TO VITAMINS AND TISSUE CULTURE

The wide distribution of bony striations leads to the suggestion that all such cases are manifestations of relative cessation of growth in length of the bone. The character of the strition is not so much influenced by the nature of the stimulus producing cessation of growth as by the duration of the stimulus. Roentgenographically and histologically the line of bony tissue will tend to be thin and compact or will consist of a band of several thin lines (embroidery effect) or of a heavy meshwork (lattice effect), according as the stimulus is acute and precise, or intermittent, or chronic and persistent. In an active patient or animal the remodelling of the bony trabeculae will be rapid; in an inactive patient or animal the remodelling may never occur. As a general rule, in man the bones at the elbow, shoulder and wrist, in accordance with greater use, will present rapid remodelling of the trabeculae and nonpersistence of the striations; at the hip, knee and ankle, especially if the patient is bedridden, the striations will tend to persist.

Bony striations are a normal feature of all animals at the time of cessation of the growth cartilages and register in bone the previous site of the epiphyseal cartilage as soon as the latter ceases to proliferate. Such striations tend to persist into extreme old age. They are veritable tombstones, marking the site of cell colonies that have passed away. Pathologically, bony striations are formed in the growing animal whenever there is cessation of growth at the epiphyseal cartilage. The density of the line tends to be proportional to the nociceptivity of the growth destroying stimulus. The persistence of the line in after life is determined by the functional use of the part. The stimulus to cessation of growth may be starvation, dehydration, an acute infection of the respiratory, urogenital or alimentary systems, or a deficiency disease such as scurvy. Experimentally, the lines can be produced in growing rachitic animals by the exhibition of cod liver oil, sunlight, ultraviolet rays, or restoration of the normal calcium-phosphorus ratio. Wherever such a line has been formed, its disappearance can be entirely or partly accomplished by functional use of the part.

Three processes are involved in normal bone formation at the epiphyseal line. Histologic examination shows, first, a zone of proliferative cartilage in which the cells exhibit the characteristic arrangement in columns or palisades, the number of cells in the normal column varying for the different animals, with a norm in the neighborhood of five. Second, there is the zone that displays calcification of the matrix and progressive degeneration of the cartilage cells. Third, there is

the zone in which osteoblasts are scattered over the trabeculae with capillary loops of the marrow blood vessels intervening. Each of these three zones is concerned particularly with one process. The first zone of proliferative cartilage is concerned purely and simply with proliferation. Adopting the terminology of Burrows,[30] it represents "a stagnant cell mass" deficient in vascular supply and is an area of minimum potential. Such a stagnant cell mass is comparable to a tumor, such as a tubercle, gumma, fibroid or cancer, in its metabolic processes, with maximum proliferation and minimum differentiation. This process of proliferation requires the substance or substances that Burrows has called "archusia," a water-soluble product that is closely related to the water-soluble growth promoting group of vitamins. The second zone, characterized by degeneration of cartilage cells and calcification of the matrix, is the area on which great light has been thrown by the experiment of Robison.[31] By exposing one half of a longitudinally sectioned tibia to a watery extract of embryonic "whole bone," Robison has demonstrated that the latter contains an enzyme that produces effective calcification of the matrix of the growth cartilages in the tibia. The processes of calcification and degeneration taking place in the cartilage bear a close resemblance to the changes that take place in tumors, especially in tubercles, gummas and fibroids. The concomitant processes of calcification and degeneration are not only a feature of morbid anatomy but also of normal growth.

The third zone is the area of active osteogenesis. Those cartilage cells which are in proximity to the blood stream become polarized and undergo rapid differentiation with liberation of active osteoblasts. Burrows has ascribed the process of differentiation at the periphery of the stagnant cell mass to the presence of a blood borne substance termed "ergusia," which is fat-soluble and closely related to vitamin A. The process of liberation of osteoblasts from the degenerating cartilage cells is a rapid explosive amitotic process comparable to that seen in spore formation in fungi and bacteria. In addition to this older theory of Ranvier regarding the origin of the osteoblasts, the possibility of osteoblasts being formed from any primitive connective tissue cell, either from the periosteum or the reticulum of the bone marrow will not discredit the characteristic of this zone, i. e., rapid multiplication and differentiation of cells for the special function of osteogenesis.

Thus, the three zones are shown to be the seat of processes that have their counterpart in normal anatomy and in morbid anatomy. The

30. Burrows, M. T.: Studies to Determine the Biological Significance of the Vitamins, Proc. Soc. Exper. Biol. & Med. **12**:241-245, 1925. Burrows, M. T., and Johnston, C. G.: The Action of Oils in the Production of Tumors, Arch. Int. Med. **36**:293-332 (Sept.) 1925.

31. Robison, R.: The Possible Significance of Hexophosphoric Esters in Ossification, Biochem. J. **17**:286-293, 1923.

three zones require, in order, a growth promoting vitamin, a calcifying enzyme, and a differentiating vitamin. The growth promoting vitamin of the proliferating cartilage closely resembles the water soluble archusia of Burrows. The differentiating vitamin of the bone area closely resembles the ergusia of Burrows.

In normal adolescence, the quantity of archusia is decreased and the stagnant cell mass of cartilage at the epiphysis ceases to proliferate. The cartilage has reached the limit of size beyond which it cannot live by imbibition of tissue juice, devoid of a definite blood supply. Calcification and degeneration take place therein under the action of the enzyme of Robison and, last, bone formation takes place under the action of ergusia. The process of bone formation is such that not only are the longitudinal trabeculae formed in true bone but cross bars of bone unite them one to the other to form a meshwork. In cases of marked athrepsia the meshwork is particularly well marked, especially as regards the transverse bars that connect the trabeculae. Their density and persistence tend to be inversely proportional to the amount of ensuing functional use of the part.

It may be asked what are the probable effects of an increase or decrease in the amount of archusia, enzyme and ergusia, respectively? An increase in the amount of archusia leads to increased proliferation of the cartilage cells and the trabeculae may increase from five cells deep to as many as twenty, i. e., rapid proliferation without differentiation, as is seen in overactive normal growth and in clinical and experimental rickets. A decrease in the amount of archusia will reduce the cartilage columns to three or even one cell, as seen in cessation of growth from any cause whatsoever, whether normal or pathologic. Such cases are shown by Tozer [25] in the study of scurvy and by Hess, McCann and Pappenheimer [23] in rats fed on what they describe as a "fat-soluble A deficient diet." The composition, character and value of this diet have been questioned by McCollum. It is an "athreptic" diet rather than a "vitamin A deficient diet."

An increase in the amount of Robison's enzyme would lead to rapid calcification of the matrix and rapid degeneration of the cartilage cells. Such an increase is seen in those animals, e. g., man, in which union of the epiphyses is concentrated into a short space of time and in which cessation of growth is rapidly brought about. Stevenson,[27] in his recent studies on epiphyseal union, has shown that cessation of growth of the long bones takes place almost entirely in the nineteenth year. On the other hand, the examination of a large number of skeletons of the rat and hedgehog has never produced a skeleton with complete epiphyseal union in all the long bones; i. e., the period of epiphyseal union

is long drawn out, as described by Alden Dawson.[32] This period of union of the epiphyses may be related to the cycle of development of the gonads. Robison's enzyme may be effective in controlling those disproportions of calcium and phosphorus which tend to produce rickets, for Park[33] has shown that the proportions of calcium and phosphorus are of more importance than the absolute quantities.

If Robison's enzyme is deficient in quantity then the calcification and degeneration will be inadequate. The calcification of the matrix may be uniformly deficient or it may be patchy. Consequently, the degree of degeneration of the cartilage cells may be uniformly deficient or may be patchy. In the so-called "florid rickets" of Wimberger,[29] the calcification is of the patchy type and is characterized in the roentgenograms by the feathery, fluffy or irregular margin that he so well portrays in this report. If the calcification and degeneration are uniformly deficient, then the edge of the calcification zone is relatively straight, devoid of the feathery tufts, and is marked by its increased distance from the bony epiphysis. This picture conforms closely to rickets of the "passive type" of Wimberger. Histologically, the calcified zone displays the same characters as seen above. If the calcification is patchy, then islands of uncalcified cartilage may be carried on into the shaft of the bone as is frequently seen in rickets of the florid type. The trabeculae are irregular in arrangement and particularly is this so near the center of the bone. If the calcification is uniform then the trabeculae are of uniform length, with poorly developed irruption of small blood vessels in them. The epiphyseal line tends to be regular and there is no marked cupping or collapse of the line.

Last, as regards the third zone, deficiency of the blood borne fat-soluble ergusia leads to failure of osteogenesis. The degenerating cartilage cells, brought into contact with the capillary tufts, fail to produce active osteoblasts and sound bone. The cells produced (whether from the chondroblasts or other connective tissue cells) resemble connective tissue cells in that they are somewhat flattened, the nuclei stain poorly, the protoplasm shows numerous basophilic granules, and fibrillar processes are marked. Bone formation is defective, connective tissue formation is excessive and roentgenographically and histologically the picture is one of osteoporosis.

The growth promoting factor necessary for the active proliferation of cartilage in the first zone is closely related to water-soluble vitamin B. Many experimenters, especially Hess,[22] reported failure to produce rickets on a diet deficient in vitamin A, and several, especially Osborne

32. Dawson, A. B.: The Age Order of Epiphyseal Union in the Long Bones of the Albino Rat, Anat. Rec. **31**:1-18, 1925.

33. Park, E. A.: The Etiology of Rickets, Physiol. Rev. **3**:106-163 (Jan.) 1923.

and Mendel,[34] showed that the addition of orange juice to the diet provided not only the antineuritic vitamin B and the antiscorbutic vitamin C but also small quantities of fat-soluble A. Goldblatt [35] has shown that orange juice, as judged by biologic experiments, contains traces of fat-soluble vitamin A. In all these experiments the animals were on an athreptic diet and did not grow. The addition of orange juice afforded the necessary growth promoting vitamin B. The animals grew and then acquired rickets because of the deficiency in fat-soluble A. Interesting light has been shed on the growth promoting water-soluble archusia by my colleague, Wright.[36] He has shown that the archusia can be separated from egg yolk by dialysis and that its activity on tissue cultures is ten times that of the nondialyzed egg yolk. Thus, although archusia and ergusia occur together in egg yolk, the water-soluble archusia can be separated from the fat soluble ergusia. The close relationship of the water-soluble growth promoting vitamin to water-soluble vitamin B and C, instead of to fat-soluble A, is thus explained. Fat-soluble A is not the growth promoting vitamin. Rachitic children are not deficient in growth promoting vitamin; athreptic children are. There is no justification for referring to fat-soluble A as growth promoting. The apparent contradictions of the experiments performed with a vitamin A deficient diet are clearly explained if this fact is grasped.

McCarrison,[37] in his classical account of beriberi has stressed the importance of the earlier manifestations of deficiency diseases as distinct from the lesions in the master tissues of the body, which are not so much signs of deficiency disease as signs of impending dissolution. The important signs of beriberi are (1) distaste for food, loss of appetite or depraved appetite; (2) gastro-intestinal derangements, indigestion, colitis and intestinal fluxes; (3) loss of weight, weakness and lack of vigor; (4) headache, anemia, tendency to edema and unhealthy skin, and (5) subnormal temperature and vascular depression. Finally, the clinical picture may be completed by the later appearance of symptoms due to malnutrition of the nervous system, the master tissue of the body. Thus, cessation of growth precedes nervous phenomena and the latter are essentially terminal as they are in such conditions as pernicious anemia, pellagra, hematoporphyrinuria and saturnine encephalopathy. It cannot be too strongly urged that the signs of deficiency in vitamin B which are looked for in most biologic experiments are signs that are acquired late and precede death, long after cessation of growth has

34. Osborne and Mendel: Proc. Soc. Exper. Biol. & Med. **19**:187-188, 1922.

35. Goldblatt, H.: A Study of the Relation of the Quantity of Fat-Soluble Organic Factor in the Diet to the Degree of Calcification of the Bones and the Development of Experimental Rickets in Rats, Biochem. J. **17**:298-326, 1923.

36. Wright, G. P.: Presence of a Growth Stimulating Substance in the Yolk of Incubated Hen's Eggs, Proc. Soc. Exper. Biol. & Med. **23**:603-605, 1926.

37. McCarrison, R.: Studies in Deficiency Disease, London, 1921, p. 65.

been established. The earlier signs enunciated by McCarrison are the real sign posts.

As regards rickets, the experiments of McCollum, Simmonds, Becker and Shipley [38] have led to the separation of the vitamin A of earlier observers into two elements. The one is a thermostable substance that is not destroyed by heating cod liver oil at 120 F. for twenty hours in excess of oxygen. This is the thermostable substance which is proved to be concerned with the calcification process and bears a close resemblance to the calcifying enzyme of Robison. It is usually referred to as vitamin X, or the true antirachitic factor. The other element is vitamin A proper, which is thermolabile, and is destroyed by heat and oxidation. This is the substance that is concerned with differentiation of cartilage cells to form osteoblasts, and it closely resembles the fat-soluble ergusia of Burrows. A deficiency of this substance leads to osteoporosis, sclerosis and disordered bone growth.

Any given case of rickets can be analyzed in terms of the three processes described: (1) proliferation of cartilage; (2) calcification and degeneration of cartilage, and (3) liberation of osteoblasts and bone formation. The roentgenographic and histologic pictures can be interpreted in such a way as to show which one or more of the processes are disordered. Park,[33] in his analysis of the low calcium and low phosphorus forms of rickets, shows that the low calcium form is characterized by evidences of resorptive activity, and cells from the fixed tissues of the body lie scattered about in the immediate vicinity of the trabeculae. Cod liver oil never restores the finer structure of the bone to the normal. The trabeculae do not become completely calcified and the provisional zone of cartilage is not always completely calcified. The bone formation will be irregular, for an adequate supply of vitamin A proper will lead to liberation of osteoblasts and normal bone formation; but defective calcification and degeneration of the cartilage with insufficient vitamin A proper or ergusia will lead to formation of those cells which might be termed osteoidoblasts. Islets of uncalcified cartilage may be carried on into the shaft. The picture is "patchy."

On the other hand, the low phosphorus form of rickets presents cartilage which is more uniformly calcified, and subsequent bone formation will depend on an adequate supply of vitamin A proper or ergusia. The picture is less "patchy."

Is the low calcium type of rickets related to Wimberger's florid type, and is the low phosphorus type related to the passive type? As recently pointed out by Chisholm,[39] in Wimberger's florid type there is

38. McCollum, E. V.; Simmonds, N.; Becker, P. J., and Shipley, P. G.: Studies in Experimental Rickets: XXI. An Experimental Demonstration of the Existence of a Vitamin Which Promotes Calcium Deposition, J. Biol. Chem. **53**: 292-312, 1922.

39. Chisholm, K.: Rickets, Brit. M. J. **1**:740-742, 1926.

a tendency on clinical examination to underestimate the amount of bone change, and in Wimberger's passive type there is a tendency, on roentgenographic examination, to underestimate the amount of bone change. In other words, the florid type is manifested particularly by obvious changes in the zone of calcification and degeneration, and the passive type is manifested by changes that are more marked in the zone of ossification. Seasonal tides of the blood phosphorus have been shown by Hess and Lundagen [40] and this seasonal tide, if dependent on the richness of absorption of ultraviolet energy, becomes an important factor in the passive type of rickets.

The pathology of bone disease has led to a series of names, and fetal bone disease, as reviewed by Ballantyne,[41] has given rise to endless names. Vrolik's [42] "osteogenesis imperfecta" is the only comprehensive name invented for all groups. It is submitted that all diseases of the skeleton, fetal and postnatal, can be analyzed and described in terms of the three processes of (1) cartilage proliferation, (2) calcification and degeneration, (3) osteogenesis. The pathology of bone can thus be interpreted in terms of disordered physiology. Such a classification has a valuable time element, for the fetal group of diseases are concerned principally with chondrodystrophy; the infantile group are concerned principally with defects of calcification, degeneration and osteogenesis, and the adult group are concerned almost exclusively with the osteogenesis involved in the remodelling and repair of adult bone in connection with absorptive phenomena and functional use.

Leg Weakness in Chicks.—The recent studies of "leg weakness" in growing chicks by Pappenheimer and Dunn [43] afford an interesting example of the genesis of the changes occurring in this disease. Roentgenographic and histologic study of the legs are reported to show no rachitic changes, but the bone shows "an arrest of osteogenesis, osteoporosis, and fibromyxomatous transformation of the marrow." The administration of the antirachitic concentrate of the nonsaponifiable portion of cod liver oil did not prevent the onset of the lesion nor modify its character. However, the addition of whole cod liver oil prevented leg weakness and brought about normal bone structure. Thus, the disease is concerned only with the process of osteogenesis, and is due to deficiency of fat-soluble vitamin A proper (ergusia).

Burrows [44] pointed out that his experiments have shown that the ergusia in the developing chick reaches a minimum at the beginning and

---

40. Hess and Lundagen: Seasonal Tide of Blood Phosphate in Infants, Proc. Soc. Exper. Biol. **19**:380-382, 1922.

41. Ballantyne: Antenatal Pathology, Edinburgh, 1904.

42. Vrolik: Tabulae ad Illustrandum Embryogenesin, Tab. XCI, Amsterdam, 1849.

43. Pappenheimer, A. M., and Dunn, L. C.: The Relation of Leg Weakness in Growing Chicks to Mammalian Rickets, J. Biol. Chem. **66**:717-729, 1925.

end of the period of incubation, with a maximum about the tenth day of incubation. Thus, at the end of the incubation period the conditions are favorable to the onset of that osteogenesis imperfecta that is due to the liberation of defective osteoblasts under the influence of insufficient ergusia or fat-soluble vitamin A proper. The curve for the variation in quantity of archusia is of the converse type with a maximum at the beginning and end of incubation and a minimum at about ten days. The chick of ten days corresponds to the human embryo of about the eighth week; differentiation has reached its maximum and henceforth the chick or embryo is concerned with growth rather than with differentiation. Organogeny is established.

The errors of growth of the first two months of human embryonic life are thus clearly differentiated from those of later life, and the conception of archusia and ergusia opens up a new basis for analyzing the causal factors in teratology. A new conception of the "time factor" is thus made possible in terms of the actual amounts of archusia or ergusia, substances that can be quantitatively assessed by their effect on tissue cultures under standard conditions of temperature, oxygen supply and rate of fluid flow. Figure 5 shows the extent to which the various processes of bone formation can be analyzed and shows the close connection between the interpretations thereof in the light of two methods of experiment, animal feeding and tissue culture. The morbid processes of bone growth can thus be interpreted in terms of disordered physiology.

Teeth and Membrane Bones.—The same processes are involved in the development of the teeth and membrane bones of the skull and face. The teeth present problems in terms of those processes of growth, calcification and ossification which can be registered roentgenographically from the sixteenth week of embryonic life to adult age. The membrane bones, involving the suppression of the intermediate stage of chondrification and calcification are characterized by failure to ossify as seen in dysostosis cleidocranialis, or by imperfect osteogenesis, as seen in craniotabes. The victim of a severe illness in childhood tends to show permanent teeth that are crowded, with deficiency of calcification in the dentine and deficiency of enamel formation in the transverse striations of the enamel of the permanent teeth.

The processes of bony absorption present the same features. Poor osteogenesis not only signifies poor osteoblasts but also poor osteoclasts, and the processes of absorption of bone involved in the growth of the air sinuses are defective. Thus, the victim of a severe illness in childhood tends to show maldevelopment of the air sinuses, recessive chin, crowded teeth with transverse striations, and an infantile type of skull.

CONCLUSIONS

1. Transverse striations in the long bones of a nonrachitic child are described and the views of Hunter with regard to growth in length stand confirmed over a period of two years.

2. Transverse striations are shown to be manifestations of cessation of growth. They occur normally in adolescence; they may occur with seasonal variations in the rate of growth; they occur in all cases of marked decrease in rate of growth from any form of acute illness or starvation: they occur as part of the healing process in rickets.

3. The skeletal processes are analyzed in terms of (1) the area of cartilage proliferation, (2) cartilage calcification and degeneration and (3) ossification proper. These three areas are related to (1) a water-soluble growth promoting vitamin or vitamins, (2) the enzyme of Robison, or vitamin X, and (3) the fat-soluble vitamin A proper.

4. These processes are discussed in terms of the archusia or growth promoting principle, and the ergusia or differentiating principle of Burrows, as enunciated for results obtained from cultures of normal and pathologic tissues.

5. A rational basis is suggested for the analysis of the processes involved in diseases of cartilage and bone, applicable to all ages.

6. The interpretations of the various "schools" concerning the agents and methods of healing rickets are considered and the fallacies of the "line test" are indicated. Cessation of growth is the important factor.

7. The term growth promoting as commonly applied to vitamin A is a misnomer. The growth promoting vitamins are water-soluble.

PRIMARY CARCINOMA OF THE THYMUS

REPORT OF A CASE *

I. I. LEMANN, M.D.
AND
JOHN SMITH, M.D.
NEW ORLEANS

The rarity of primary carcinomas of the thymus is indicated by the fact that only three cases have been reported since the article of Rubaschow [1] in 1911. He had gathered from the literature reports of sixty-nine tumors of the thymus, fifty-two sarcomas, twelve carcinomas and five undetermined growths. A further search of the literature has revealed another carcinoma reported by Pollosson and Piery [2] in 1901 (apparently overlooked by Rubaschow), one by Honda and Taguchi [3] in 1921, one by Symmers and Vance [4] in 1921 and one by Jacobson [5] in 1923. The case herewith reported is therefore the seventeenth primary carcinoma of the thymus recorded.

REPORT OF CASE

History.—A. L. L., aged 58, a traveling salesman, came under observation, Feb. 5, 1925. For three months he had had constant pain in the left hypochondrium and lumbar region. There had been constant pain in the right side for about two months. For two months heaviness in the epigastrium came on after eating or drinking, even of water. The appetite was poor, and he ate only soft food. The pains were so excruciating that he did not feel like eating. However, he had no nausea and no vomiting. He thought he had lost a little weight. He had no cough but expectorated a small piece of mucus in the morning. There was no shortness of breath, no palpitation. The past history was not particularly interesting. He could not recall any diseases of childhood nor had he been seriously ill during his adult life. Many years before he had had gonorrhea, which was followed by stricture, and he had been treated for "bladder trouble" three years before and had gone for prostatic massages from time to time. The family history is of significance only in that two sisters had died of carcinoma.

Physical Examination.—The physical examination showed a poorly nourished, small man, 5 feet 3 inches tall, weighing 118¾ pounds (53.8 Kg.). He was evidently in great pain and walked into the office holding his side and back,

* From the department of medicine, Tulane University of Louisiana School of Medicine, and from the pathologic service, Touro Infirmary, New Orleans.

1. Rubaschow: Eine boesartige Thymusgeschwulst, Virchows Arch. f. path. Anat. **206**:141-157, 1911.

2. Pollosson and Piery: Un cas d'epithelioma primitif du thymus; tumeur polykystique congenitale du cou chez un enfant; epithelioma infiltre, Province méd. **15**:1-4, 1901.

3. Honda, I., and Taguchi, K.: Ueber primare bosartige Geschwulste des Thymus, Gann **15**:57-59 (Dec.) 1921; abstr., J. A. M. A. **78**:772 (March 11) 1922.

4. Symmers, D., and Vance, B. M.: Epithelioma of Thymic Origin, Arch. Int. Med. **26**:239 (Sept.) 1921.

5. Jacobson, V. C.: Primary Carcinoma of Thymus, Arch. Int. Med. **31**: 847-856 (June) 1923.

bending somewhat forward. The skin was dark olive (normal). There was no adenopathy. The mucous membranes were normal. The tongue was slightly coated and the teeth were poor. The tonsils were negative; the lungs were normal; the heart was of normal size. The dulness measured 8 cm. from the midline in the fifth intercostal space, 2 cm. to the right. There was no retrosternal dulness. The heart rate was 100. The blood pressure was 120 systolic, 70 diastolic. There was no murmur and no irregularity. There was marked peripheral arteriosclerosis. The abdomen was slightly enteroptotic. The liver was felt two fingerbreadths below the costal margin. The spleen was not felt. The pupils were equal, regular, symmetrical, and reacted to light and accommodation. The knee jerks were normal. The dorsolumbar spine was very stiff. The urine showed hyaline casts and a few leukocytes. The red blood cells showed no abnormality. The hemoglobin was 95 per cent. The Wassermann reaction was negative.

Treatment and Course.—The back was strapped, and this afforded great relief. After ten days it was necessary to remove the strapping because of skin irritation. At this time a skiagraph of the spine was taken and the radiologist reported that there was evidence of hypertrophic arthritis of the spine. A plaster jacket was applied by Dr. E. S. Hatch, March 2. This, however, afforded the patient little relief and it was necessary to give him acetylsalicylic acid and codeine. He walked around for nearly a month wearing the cast, complaining always of excruciating pain. April 3, he was readmitted for observation because there was marked edema of the right leg and foot and some of the left leg. Because of this the cast was removed, April 7. April 8, the following note was made: "There has been a constant grunting and complaining since his admission. While he says he cannot sleep, very often sleep has been induced by hypodermics of sterile water or by sugar capsules. At others times phenobarbital has been used. The edema of the lower extremities has continued, much more marked on the right than on the left. Last evening the cast was removed by Dr. Hatch because of the patient's constant complaint of its pressure. This morning he declares himself free of pain but complains of weakness of the whole body, especially of the back." The querulousness still continued. The edema gradually disappeared after the removal of the cast. Apparently the edema had been due to pressure on the femoral veins. The patient continued to complain constantly, "I can't get a comfortable position. My body has no strength. I have pain in the back and right knee." April 17, the report was, "There is no doubt that the patient has grown considerably weaker. He has complained constantly of this weakness and pain in the right knee. He is made to stand up for the first time since the cast was removed and there is now evident in the left interscapular space a tumor about the size of an orange from about the level of the seventh to that of the ninth or tenth dorsal vertebrae. To the outer and upper side of this tumor there is exquisite tenderness; over the swelling itself, dulness and diminished respiratory sounds. Just beyond it toward the scapular side the respiratory sounds are exaggerated." Fluoroscopic examination showed a large pulsating mass in the chest. This was interpreted by the roentgenologist as an aneurysm. It was thought, therefore, that his pains might be explained on the basis of an erosion of the spine. The patient continued to lose strength and weight and to complain constantly of excruciating pain in the back. The temperature, which had been normal in February and March, began in April to show frequent elevations to the neighborhood of 100 F. This rise later became a daily occurrence. April 12, the hemoglobin had fallen to 65 per cent and the red blood count was 4,080,000. There was a slight anisocytosis. The leukocyte count was 10,750; neutrophils, 81; small lymphocytes, 18, and eosinophils, 1. April 20, the red cells had fallen to 3,565,000; the hemoglobin remained 65 per cent; the leukocyte count was 13,000. The neutrophils totaled 79; the small lymphocytes, 10; the eosinophils, 3, and the basophils, 1. The urine continued to show hyaline and an occasional granular cast but no other abnormality. April 28, the report read, "In the last few days a second protuberance has developed in the back. This second protuberance is on the right side

opposite the tenth and eleventh ribs. It is exquisitely painful. Edema of both feet and both legs is present, more marked on the right." It was apparent that an aneurysm could not proceed as rapidly as this and that there could be but one explanation of the appearance of the masses in the back, namely, that they were metastases. It was believed, therefore, that the mass seen in the chest was not an aneurysm but a neoplasm. A skiagram made at this time was reported as showing a large neoplasm involving the entire mediastinum. The patient continued to grow weaker and more emaciated. The tumors grew larger, more superficial and more fluctuating. The skin became edematous. They were sensitive but not extremely so. There was no pulsation and no thrill over them. June 27, the upper one on the left extended from about the level of the sixth or seventh vertebra to that of the ninth dorsal vertebra. The lower one on the right extended from about the ninth or tenth dorsal vertebra to the first or second lumbar. The patient continued to have a slight daily rise of temperature—from 99.5 to 100 F. He

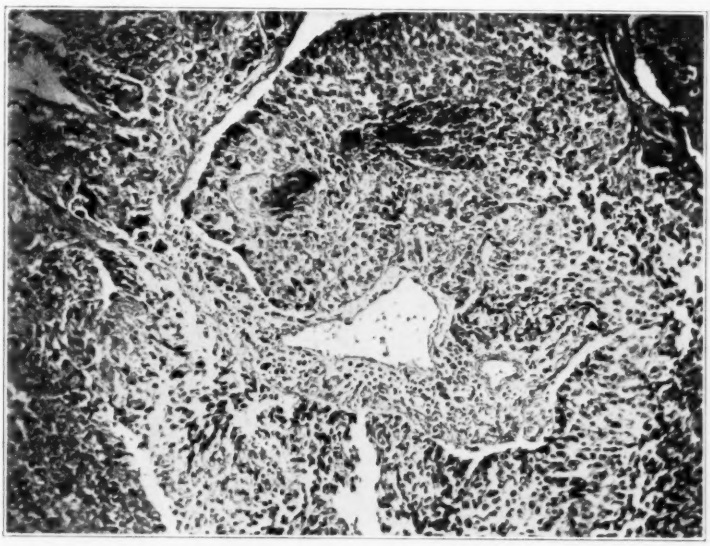


Fig. 1.—Retropleural metastasis, under low power; Hassal's corpuscle shown above and to the left of the center; in the dark in the upper center staining is a collection of small round cells; large polyhedral cells in chains and sheets form the bulk of the picture; in the center is a lymph space.

suffered a great deal from pain in the back and a burning sensation all around the middle of the body. It was necessary to give him morphine in increasing doses up to 1.5 grain daily. At times he expectorated bloody mucus. The weakness grew progressively greater so that he slept most of the time. He came to a point where he ate practically nothing. For the last three or four days of his life he had retention of the urine and it was necessary to catheterize him. He was conscious practically to the end. About one-half hour before death, he was given a gruel; he choked, vomited and was prostrated from exertion. From this he passed into the final unconsciousness.

Necropsy.—The body was that of a fairly well developed but poorly nourished white man, measuring about 5 feet 3 inches and weighing about 95 pounds (43.1 Kg.). The skin was sallow, rather soft and pliable. Postmortem rigidity and

lividity were absent. The pupils were equal and measured about 7 mm. On the posterior surface of the thorax was a semifluctuant mass on the right side involving the ninth, tenth and eleventh ribs immediately anterior to their attachments to the vertebrae. On the left side was a similar mass about 6 cm. in width by 10 cm. in length involving the seventh, eighth and ninth ribs. An attempt at aspiration with forcible suction obtained a very small amount of thick caseous necrotic material. Superficial lymph nodes were palpable but not enlarged. The abdomen was flat.

Pleural Cavity: The sternum was found firmly adherent to an underlying mass extending from the episternal notch to the level of the fifth rib. Both pleural cavities were filled with an amber fluid. There were a few adhesions in both right and left apexes. The mediastinum was occupied by a large tumor mass measuring 12 cm. in length by 10 cm. in breadth which extended from the sternal

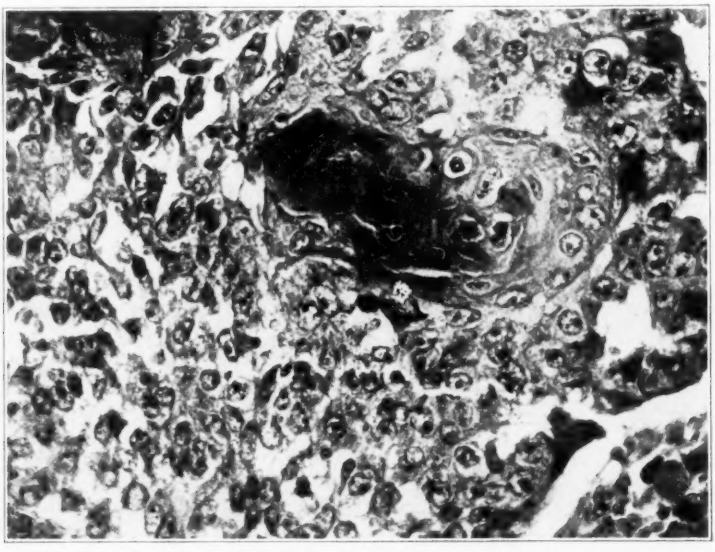


Fig. 2.—Part of the field of figure 1, showing detail of Hassal's corpuscle, under high power.

notch and pressed on the base of the heart, forcing that organ downward. This mass was adherent to the parietal pleura on both sides and to the pericardium beneath. It was firm in consistency for the most part although here and there were found fluctuating areas which were filled with clear amber fluid. It was growing around the great vessels of the heart. On section it showed considerable resistance to the knife and presented a dirty yellow cut surface. It appeared to be made up largely of dense connective tissue with here and there groups of cells less firm in consistency, some of which showed dirty yellow necrotic areas. After the removal of the lungs an oval semifluctuant mass was found in the right pleural cavity corresponding to the mass described on the external surface. This mass was covered by pleura and on sectioning was found to be a secondary neoplasm that had destroyed the ninth, tenth and eleventh ribs from the angle of their attachment to the spine. The laminae of the corresponding vertebrae were destroyed and replaced by the new growth, with the result that there was a communication with the spinal canal. On the left side was a similar mass involving the seventh, eighth, ninth and tenth ribs.

Pericardial Cavity: The pericardial cavity was pressed on by the tumor mass above described and its anterior wall was thickened by this tumor mass. The inner surface was smooth. On both sides of the pericardium, particularly on the right, there was a varix of dilated veins measuring 2 by 3 cm. The heart was relatively small and its outer surface showed no pathologic changes. It was dark brownish red.

Lungs: The right lung at its apex showed a few areas of healed tuberculosis and on its upper surface were tags of adhesions. It was adherent also in its middle and upper lobes to the growth in the mediastinum and also to a tumor mass in the posterior chest wall. It was rather doughy in consistency and with the exception of a small amount of edema was negative. The left lung showed a similar condition to the right. The peribronchial lymph nodes were somewhat enlarged but on section showed no macroscopic evidence of neoplasm.

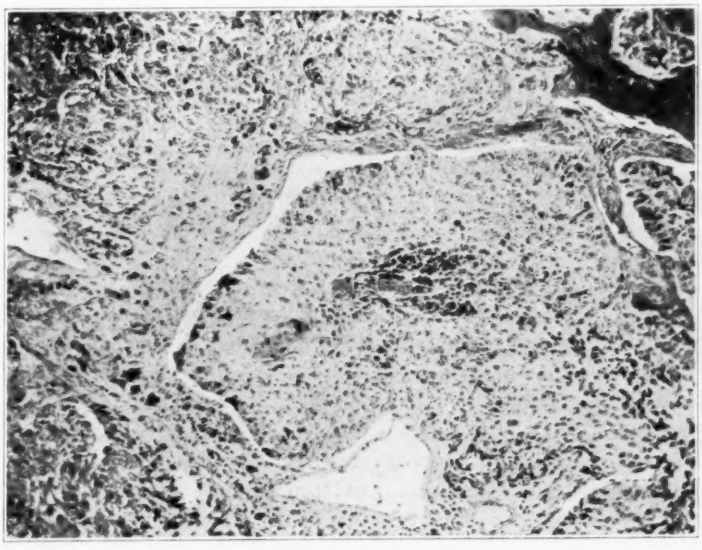


Fig. 3.—Metastasis eroding the vertebrae, under low power; bone is shown in the upper right corner.

Abdominal Cavity: This was free from fluid or evidences of an inflammatory reaction. The omentum covered the intestines and was adherent by old adhesions to the cecum and adjacent wall. The liver was pushed downward, its lower border being on a level with the umbilicus. The lesser abdominal cavity was negative.

Spleen: The spleen measured 10 by 6 cm. and weighed about 120 Gm. It was firm in consistency and was adherent by old adhesions to the surrounding tissue. On sectioning it offered increased resistance to the knife and the cut surface showed an increased amount of connective tissue. The pulp was rather firm, maroon, and did not readily come off to the knife. The malpighian corpuscles were not prominent.

Liver: The liver measured 25 by 18 by 10 cm. It was dark brown, somewhat mottled in appearance and rather smooth for the most part, although there were noted several secondary new growths that produced irregularity in contour. One was situated on its anterior surface just below the dome in the midline of the right lobe. Another was found on the inferior surface of the left lobe. On

section the liver presented a nutmeg appearance. A number of small pinkish gray areas were present throughout the structure in addition to the masses visible on the outer surface. These masses were rather circumscribed, more or less spherical in outline, and in addition to their pinkish gray color showed many foci of necrosis.

Pancreas: This was normal.

Suprarenals: The suprarenals were normal.

Kidneys: Both kidneys presented the same picture. They were buried in a mass of firm perirenal tissue and were quite firm in consistency. When the capsule was peeled off, it was adherent and left an outer surface that was rough and irregular presenting the picture of persistent fetal lobulations. On section the kidneys offered increased resistance to the knife and showed some thinning of the cortex and an increase generally of connective tissue. The parenchyma was dirty yellow.

Prostate: The prostate was normal.

The anatomic diagnosis was primary neoplasm of the thymus; secondary neoplasm of the liver, lungs and bones; chronic interstitial nephritis; chronic splenitis; passive congestion of the liver, and pleural effusion.

The microscopic diagnosis was neoplasm of the mediastinum, that is, carcinoma of the thymus gland characterized by the presence of Hassal's corpuscles; in the lungs, bronchopneumonia; chronic pleuritis and anthracosis; secondary neoplasm (thymus); in the bone, secondary neoplasm ((thymus); in the liver, fatty degeneration, passive congestion, and secondary neoplasm (thymus); in the kidneys, chronic interstitial nephritis and cloudy swelling; in the spleen, fibrosis, pigmentation and passive congestion. The pancreas was normal. The intestines showed degeneration of the mucosa and localized areas of congestion.

COMMENT

Ewing[6] has remarked, "No group of tumors has more successfully resisted attempts at interpretation than those of the thymus." Even a cursory review of the literature reveals the confusion that has existed. Some authors have evaded definite classification and have been satisfied to state the evident malignant nature of the growth. Ewing has made two main groups: (1) lymphosarcoma or thymoma, arising probably chiefly from the reticulum cells and probably lymphocytes, and (2) carcinoma arising from the reticulum cells. He calls attention to the varying nomenclature employed by different writers and to the existence of apparent transitional forms connecting the two types. It is significant, he remarks, that carcinomas have been recorded almost entirely by the French, while practically all the German reports have been of sarcomas. Some of the authors have described as carcinomas tumors that have many of the features designated by others as those of sarcoma. The lymphosarcomas are often encapsulated tumors occupying the mediastinum. They may, however, present extensions by continuity and may metastasize to other viscera or to the bone. The microscopic picture varies greatly but most of these tumors (lymphosarcomas) fall into one of three groups:

---

6. Ewing, J.: Report of Three Cases of Thymoma, Surg. Gynec. Obst. **22:** 461 (April) 1916.

A. Tumors showing many small round cells and plasma cells and some large polyhedral cells, suggestive of the granuloma cells of Hodgkin's disease.

B. Tumors showing a large number of polyhedral cells with comparatively few of the small round cells. These tumors have been classified by some of the French as carcinomas.)

C. Tumors in which the large polyhedral cells tend to form sheaths about the blood vessels, suggesting, therefore, the diagnosis of perithelioma.

When these tumors show metastases the large polyhedral cells are the ones most commonly seen in the secondary growth. At times they tend to form structures simulating Hassal's corpuscles. The gross picture of carcinomas of the thymus is similar to that found in the harder of the lymphosarcomas but metastases are more common. There is also usually more dense connective tissue stroma with islands of isolated cells. There are areas of necrosis with a tendency to cyst formations. The flat or polyhedral cells are arranged in cords, sheets and islands. There is a rather marked tendency to form Hassal's corpuscles and at times structures resembling glandular acini. As a rule, the small round cells are relatively few and the connective tissue stroma is dense. The large polymorphonuclear cells observed in these tumors are of two types: (1) cells with a single nucleus and pale staining acidophilic cytoplasm, often showing vacuolization, and (2) cells with a deeper staining, more opaque acidophilic staining cytoplasm with multiple vesicular nuclei. Concentric layers of cells with flattened or elongated outlines and nuclei form structures resembling Hassal's corpuscles.

The neoplasm in our case was designated a carcinoma primary in the thymus because the primary growth was in the anterior mediastinum, appeared to spring from the thymus, did not show direct continuity with contiguous structures and presented the following features:

Gross.—(*a*) A rather firm tumor occupying the anterior mediastinum and pushing the heart downward and showing some fluctuant cystlike areas.

(*b*) A cut surface, of dirty yellow color, presenting a dense connective tissue stroma that separated islands of cells. There were many yellow necrotic areas.

(*c*) Secondary growths on the posterior chest walls to the right and left of the vertebral column. These growths showed no direct continuity with the primary tumor. Metastases to the liver and the lungs which were rather well circumscribed and cellular in nature.

Microscopic.—(*a*) In the primary tumor were sheets and cords of cells, mostly large polyhedral cells, showing many structures resembling

Hassal's corpuscles. These cell groups were well surrounded by a dense connective tissue stroma. There were few small round cells in the primary growth. Fluctuating structures were apparently due in part to degeneration and in part to secretion. Tendency to form acini was rather marked in the primary growth.

(*b*) The picture in the secondary growths was similar to that seen in the primary growth but there were fewer small round cells and a less dense connective tissue stroma. Hassal's corpuscles were present here in moderate numbers. In the secondary growths on the chest wall the tendency to form acinus-like structures was marked. In the liver growth little of this tendency was noted.

The present case is of interest not merely as a rarity but as pointing certain definite clinical lessons. It was apparently impossible to make a diagnosis of intrathoracic neoplasm at the time that he first came under observation. He had at that time no symptoms pointing to intrathoracic disease and yet we must believe that the growth had already metastasized into the lumbar vertebrae. The excruciating pain of which he had been complaining for three months can be explained only in this manner. The roentgenograms taken of the spine at that time showed no indication of this metastasis but merely a hypertrophic arthritis which undoubtedly coexisted. Nor would one have been apt later on to make a diagnosis of the thoracic growth on the basis of physical signs even when we were quite sure from other evidence that the disease did exist. It was only at the very last of the illness that he expectorated bloody mucus. There was at no time evidence of pressure on the trachea nor on the bronchi nor on the vena cava and other large vessels; nor was there displacement of the heart. All this seems remarkable in view of the size and position of the neoplasm as discovered at necropsy. The belief that the mass seen fluoroscopically was an aneurysm lasted but a few days. It would have been extraordinary to see an erosion by an aneurysm advance so rapidly. When, however, the second fluctuating mass appeared an erosion of this character could no longer be accepted. The parallelism between Jacobson's case and ours is most striking. In his case, too, the presenting symptom was that of pain and stiffness in the lower part of the back. A plaster jacket was later necessary. The general course of his case was very much like that of the case reported here. The necropsy revealed a thymic growth with metastases into the lungs and into the vertebrae. The primary growth differed from ours in being comparably small.

SUMMARY

In the case of primary carcinoma of the thymus with metastases into the lungs, the liver and the vertebrae reported here, the presenting symptom was pain in the back. The diagnosis of malignant intrathoracic

disease was made possible only by the appearance of evident metastases in the back and the discovery by roentgen ray of a shadow in the thorax. The intrathoracic growth gave rise to no local signs or symptoms. It is suggested that the possibility of thymus neoplasm be borne in mind when there is roentgenographic evidence of abnormality in the mediastinum. The possibility of this diagnosis is strengthened when metastases are found.

THE SPECTROPHOTOMETRIC ANALYSIS OF THE COLOR OF THE SKIN

AND THE OBSERVATIONS BY THIS METHOD IN NORMAL AND IN PATHOLOGIC SUBJECTS *

CHARLES SHEARD, PH.D.
AND
GEORGE E. BROWN, M.D.
ROCHESTER, MINN.

As Rowntree and Brown [1] have stated in a recent article, there is a pressing need in clinical medicine for a method of measuring and recording the color of the skin. A diversity of terms and descriptive expressions exists in clinical literature in the varied attempts to state the color of the skin and its changes during the progress of the treatment of the patients under observation. For example, various clinicians have recorded the color in polycythemia as being "red," "brick red," "congestive red," "reddish cyanosis" and even "cyanotic." Our knowledge of color and color vision is fundamentally inexact and as a result the language of color, while it may be beautiful, lacks precision. For there are myriads of shades of red from the faintest pink to the darkest red, and yet they are all to be classified as being reds. The terms ordinarily used to describe color do not connote the same conceptions. And, again, it is well nigh impossible for any two pairs of physical eyes and sets of mental receptor organs to see the same "thing" or the same attributes of the "thing," whatever this may be. Furthermore, pigments and spectral colors are vastly different. The spectral colors of white light, such as sunlight, are pure colors, can be measured in intensity and purity and so on, and are, therefore, readily standardized. For instance, spectral yellow of a given wave length (say 590 millimicrons, or sodium yellow) is always the same yellow and can be exactly reproduced.

METHODS OF COLOR ANALYSIS

Two possible methods of analysis of the color of the skin are available: first, a comparison with color plaques, such as has been developed by Rowntree and Brown [1] in their universal skin tintometer of nine separate color scales which can be subjected to analysis by the Munsell [2]

---

* From the Section on Physics and the Division of Medicine, Mayo Clinic and the Mayo Foundation.

1. Rowntree, L. G., and Brown, G. E.: A Tintometer for the Analysis of the Color of the Skin, Am. J. M. Sc. **170**:341-348 (Sept.) 1925.

2. Munsell, A.: A Color Notation, ed. 6, Baltimore, Munsell Color Company, 1923.

system of color measurement, and, second, a spectrophotometric analysis of the color of the skin. Tintometric or colorimetric methods of estimating and recording color are doubtless of value in the practice of medicine. Such systems of classification as applied to color are of some aid in the diagnosis and in the course of the treatment of diseases in which appreciable color changes occur in the skin, as in jaundice, cyanosis, polycythemia vera, anemia, Addison's disease and hemochromatosis. However, such methods do not in any wise analyze the spectral light reflected by the skin and therefore cannot record in terms of the three attributes of color, brilliance, hue and saturation.

It is a well known fact in physiologic optics that white light can be spectrally made out of certain quantities of red, green and blue of limited wave length values or, again, out of certain quantities of orange, green and blue of limited wave length values, according to the color tables of Maxwell [3] and others.[4] Hence, the expression "white light," in and of itself, states nothing about the components and the amounts thereof which go to make up the white light. And again, the definition of Addison's disease states that "it is a disease characterized by a bronzelike pigmentation of the skin." [5] The expression "bronzelike" is very inexact, since nearly all of us have bronzelike coloration of the skin but this varies considerably in the quantity and distribution of the pigment, as will be shown later in the results recorded in this article. For a normal blonde, a normal brunette, a negro and a person suffering from Addison's disease differ from one another only in the amount of pigmentation, which is in large part melanin. Ordinarily, the degree of pigmentation is to be roughly thought of as a smoke screen (in some persons very slight and in others very dense) laid down between solar radiation, on the one side, and the blood in the peripheral capillaries on the other side of the dividing medium, the epidermis.

The three attributes of color are relative luminosity (brilliance), dominant wave length (hue) and purity (saturation). The percentage brightness of a color defines how much of the total amount of standard white light (sunlight or its equivalent) which falls on it any color is capable of reflecting (or transmitting). By the hue or dominant wave length is meant that attribute of the color which permits it to be classed as reddish, yellowish, greenish or bluish. Percentage of purity or

3. Maxwell, J. C.: On the Theory of Compound Colors and the Relations of the Colors of the Spectrum, Scientific Papers **1**:410-444.

4. Sheard, Charles: Physiologic Optics, Being an Essay Contributed to the American Encyclopedia of Ophthalmology, Chicago, Cleveland Press, 1918, vol. 13, pp. 9720-10214.

5. Dorland, W. A. N.: The American Illustrated Medical Dictionary, ed. 12, Philadelphia, W. B. Saunders Company, 1923.

saturation determines the degree of hue. Thus, the percentage of purity defines how red or how yellow, and so forth, a color is.[6]

Our complexions and the colors of our skins are dependent on a variety of causes. According to Lundsgaard and Van Slyke, the main factor that contributes to the production of cyanosis is the absolute amount of hemoglobin and the erythrocytes present in the peripheral vessels. This is subject to a group of modifying factors: (1) the area of exposure of the capillary blood, which depends on the number of open capillaries for each unit of surface area and the area of the exposed portion of the loops;[7] (2) the thickness and pigment content of the epidermis; (3) the color of the blood plasma, either in the blood or in the tissues; (4) the color effect of the visible venules, which is related to their position with reference to the heart level,[8] and (5) the variation in the oxygen unsaturation. The same factors hold true in a large

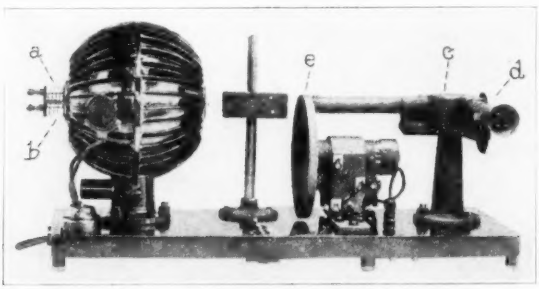


Fig. 1.—The spectrophotometer, or color analyzer.

degree for color of the skin in general. Normal blondes and brunettes, for instance, differ only in the amounts of pigmentation. It is said: "That the pigmentation of the skin bears some relation to health is well recognized. Tanned individuals are generally healthy. But whether the reaction is a direct or indirect one is unknown."[9] We believe, however, that the condition of tan per se, which is due to the deposit of pigment, is not necessarily such an indication of health, because of the fact that the blood (by reason of the reflection of light from the blood in the capillaries at the surface of the skin) contributes its quota to the composite color of the skin as seen by the eye.

6. Report of Committee on Colorimetry, L. T. Troland, Chairman: J. Optical Soc. Amer. **6**:527-596, 1922.

7. Brown, G. E., and Sheard, Charles: Measurements on the Skin Capillaries in Cases of Polycythemia Vera and the Rôle of These Capillaries in the Production of Erythrosis, J. Clin. Investigation **2**:423-434 (June) 1926.

8. Goldschmidt, S., and Light, A. B.: Cyanosis Unrelated to Oxygen Unsaturation, Produced by Increased Venous Pressure, Am. J. Physiol. **73**:173-192 (June) 1925.

9. Mathews, A. P.: Physiological Chemistry, ed. 4, New York, William Wood & Co., 1925, p. 711.

The eye is a poor instrument for analyzing or resolving the constituents of color. Spectrophotometric analysis of the light reflected by the skin and the subsequent further analysis of these data into red, green and violet excitation color values and relative luminosity values of the noonday sun as a standard, furnish the only strictly scientific means of obtaining information concerning the rôle played chiefly by pigment and blood in the color of the skin. So far as we know, no work has been done previously on this subject by such methods.

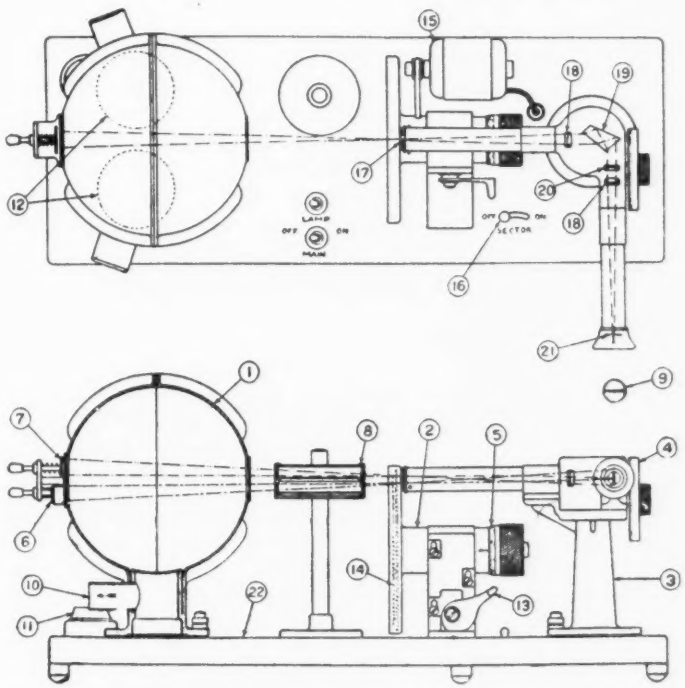


Fig. 2.—Cross-section diagrams showing the working parts of the spectrophotometer, of which the following are noted: (1) spherical light source; (2) photometer; (3) spectrometer; (4) wave length scale; (5) photometer scale; (6) holder for standard sample; (7) holder for reflection samples; (9) field of view through the eye slit; (14) sector disks; (17) entrance slit; (19) dispersion prism, and (20) biprism.

SPECTROPHOTOMETRIC METHODS AND PROCEDURES

The spectrophotometer used in these investigations was one brought out recently by Keuffel [10] and Esser and referred to in the literature as a "color analyzer." Figure 1 is a reproduction of a photograph of the

10. Keuffel, Carl: A Direct Reading Spectrophotometer, J. Optical Soc. Amer. **11**:403-410, 1925.

instrument. Figure 2 is a cross sectional diagram showing the working parts of the machine and their arrangement as to the spectrometric and photometric operations. The instrument consists essentially of a lamp house carrying two magnesium blocks, *a* and *b* (fig. 1), cut from the same block, which are placed at the rear; these blocks serve as sources of light for transmissions through receptacles containing various liquids which may be introduced into the paths of light. In these experiments, however, we are dealing with percentages of reflection rather than transmission. The magnesium block *b* (fig. 1) is therefore allowed to remain in place and the block *a* is removed and in its stead is placed the object (such as a finger, or the back of the hand) which is to be examined spectrophotometrically as regards its reflecting powers. The two beams of light reflected by the block *b* and the hand (placed at *a*) enter the spectrometer *c* (fig. 1). The spectrometer proper does not differ in fundamental principles from the ordinary constant deviation type of instrument except for the addition of a biprism, which is placed in front of the telescopic lens system, and an observing (exit) slit in the eyepiece. Throughout the series of observations which are being reported in this article, the exit and entrance slits were kept at constant or fixed values, following the initial adjustment of the entrance slit to give 100 per cent transmission from the two magnesium blocks throughout the whole spectrum.

The method of getting the data shown in figures 3 to 6 is as follows: White light from two 400-watt stereopticon bulbs in the lamp house, after reflection from the block *b* and the fingers or portion of the hand placed at *a*, is admitted to the spectrometer The spectrometer, *c* (fig. 1), is set at any desired wave length by means of a calibrated wheel, *d* (fig. 1). As an illustration, with a setting at 590 millimicrons (which is close to the sodium yellow of the spectrum) the observer, on looking through the exit or eye slit, sees two semicircular colored areas in juxtaposition, with the dividing line horizontal. Both halves of the circle will have the same hue (yellow) but not necessarily the same brightness or saturation value. The adjustment for the equality of brightness, or a match, is then made by varying the size of the sector opening in the rotating sector, *e* (fig. 1), placed in front of the spectrometer, *c* (fig. 1), until the two halves of the field are equally illuminated. The percentage reflection of light from the fingers (or hand) for any given wave length is read directly from a calibrated drumhead. This drumhead is mechanically connected to the sectored disks in such a manner as to permit of the rapid turning of it by hand, thus providing a quick way of varying the relative proportions of open and closed sectors.

The data on spectrophotometric reflection from portions of the body other than the fingers, such as the back of the hand or the palm

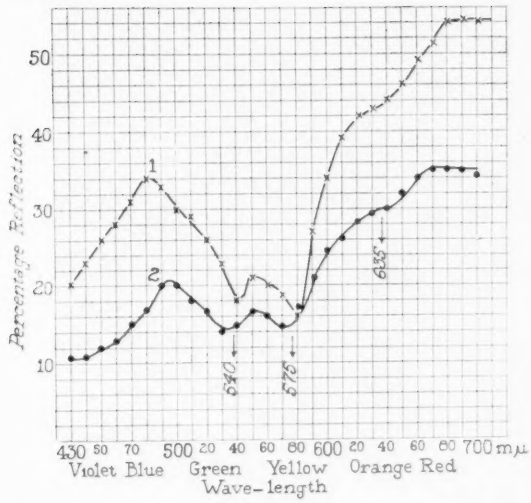


Fig. 3.—Spectrophotometric reflection curves: curve 1, a normal blond; curve 2, a case of Addison's disease. The absorption bands at 540, 575 and 635 millimicrons (or thereabouts) in these curves as well as in those of figures 4 to 6 should be noted. The middle and ring fingers were used for obtaining spectrophotometric reflection curves in all conditions, both normal and abnormal, which are presented and discussed in this article.

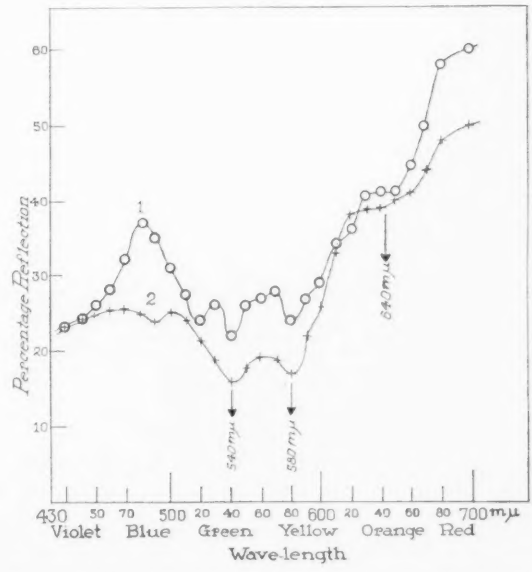


Fig. 4.—Spectrophotometric reflection curves in a case of polycythemia vera: curve 2, before treatment with phenylhydrazine, and curve 1, three weeks after treatment was instituted.

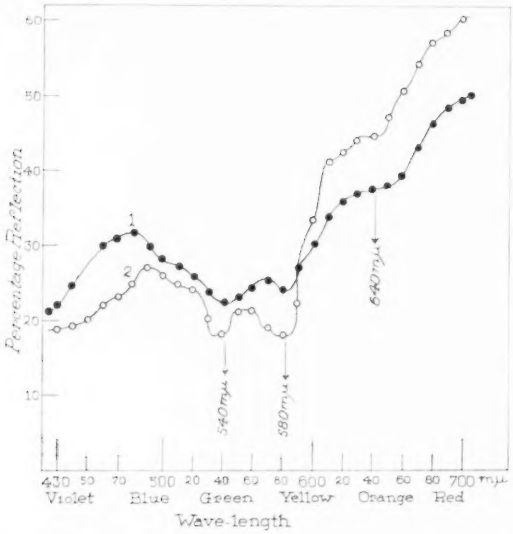


Fig. 5.—Spectrophotometric reflection curves in a case of polycythemia vera: curve 2, before treatment with phenlyhydrazine and curve 1, one month after the commencement of the treatment with phenylhydrazine.

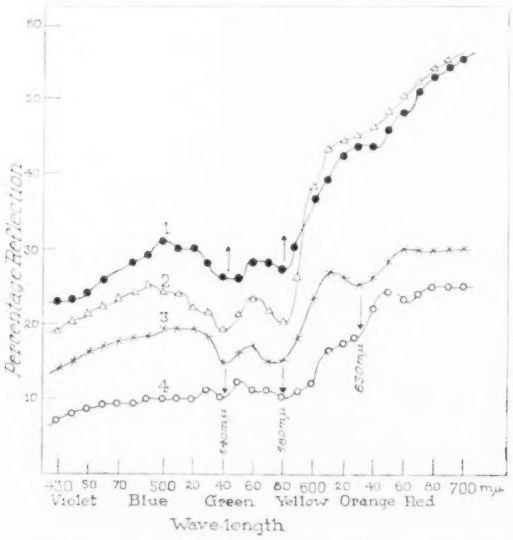


Fig. 6.—Spectrophotometric reflection curves: curve 1, normal female brunette; curve 2, normal male brunette; curve 3, a case of scleroderma, and curve 4, a normal mulatto.

of the hand, may be obtained with this instrument by a slight modification that we have introduced to take the place of the plate holding the blocks *a* and *b* (fig. 1). We have substituted a concavoconvex metal screen with its concave side turned away from the lamp house proper. A block of plaster-of-paris covered with magnesium oxide paint serves as the standard *b* (fig. 1), and a portion of the face, arm or body may be placed opposite the opening *a*.

SPECTROPHOTOMETRIC REFLECTION: CURVES IN CERTAIN NORMAL AND PATHOLOGIC CONDITIONS

Figures 3 to 6 give selected spectrophotometric reflection curves. The legends accompanying these figures give the explanatory data. In every instance the reflection curves were obtained from the middle and ring fingers of the left hand. In figure 6 are plotted percentage reflection data for a normal blond (curve 1), a normal brunette (curve 2),

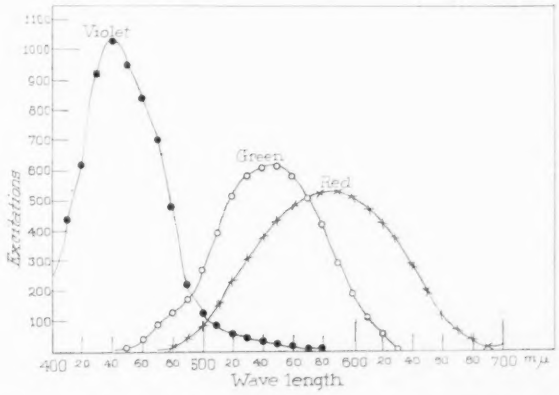


Fig. 7.—Elementary color excitations for different wave lengths.

a negro (curve 4), and a person who had scleroderma (curve 3). An experienced eye might be able to take such a group of curves and to draw the correct conclusion that the only difference in these cases was in the amount of pigment present. In all the curves of these figures there are indications of three absorption regions or spectral bands of lower percentages of reflection from the surface of the skin: one in the red at approximately 630 to 640 millimicrons, due without doubt to hematin in the tissue cells, and two bands in the yellow-green region, 570 to 580 millimicrons and 530 to 540 millimicrons, which are due to the oxyhemoglobin absorption of light by the blood.

Figures 4 and 5 present the spectrophotometric reflection curves from the fingers of patients suffering from polycythemia vera. In each figure curve 2 represents the results before treatment with phenyl-

hydrazine, while curve 1 gives the spectrophotometric data after treatment. In both instances it can be seen that the percentage reflection is considerably increased in the region 450 to 580 millimicrons (blue to yellow) after treatment with phenylhydrazine.

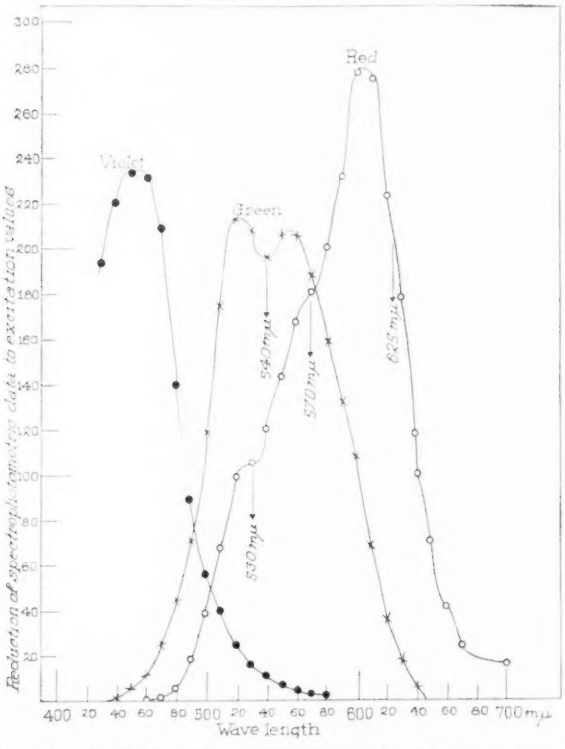


Fig. 8.—Analysis of the spectrophotometric reflection data from a normal blond (fig. 3, curve 1) into the three primary color excitation curves.

ANALYSIS OF SPECTROPHOTOMETRIC DATA INTO COLOR EXCITATION VALUES

Probably the most fundamental of all the psychologic data relating to color are the three color excitation curves, which represent the laws of three color mixture. Extant data on these relationships are due to Maxwell,[3] Abney [11] and König and Dietrici.[12] The results of the

11. Abney, W. de W.: Researches in Color Vision and the Trichromatic Theory, London, Longmans, Green & Co., 1913.

12. König, A., and Dieterici, C.: Die Grundempfindungen in normalen und abnormalen Farbensystemen und ihre Intensitätsverleitung im Spektrum, Ztschr. f. Psychol. u. Physiol. d. Sinnesorg **4**:241-347, 1892.

latest investigations on this matter, reduced to an equal energy spectrum and referred to average noon sunlight, are plotted in figure 7.

Spectrophotometric data are generally given in the form of curves of spectral transmission or reflection. Such curves require combination with a certain energy distribution (representative of the particular

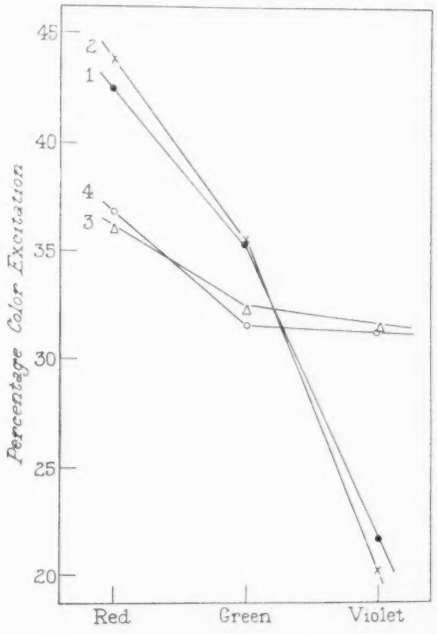


Fig. 9.—Percentage color excitation values as determined from the summation of the data obtained from the elementary color excitation curves: curve 1, normal blond; curve 2, normal brunette; curves 3 and 4, cases of polycythemia vera.

source by which the object is viewed) in order that they shall become determinative of a definite color. The process of reducing any given set of spectrophotometric specifications to excitation values is therefore as follows: (1) Multiply each of the ordinates of the transmission or reflection curve by the corresponding ordinate of the energy distribution curve of the source; (2) multiply each of the ordinates of the resulting curve by the corresponding ordinate of each of the color excitation functions as shown in figure 7, this being a separate operation for each of the three excitations and yielding three separate curves which represent the respective excitation values for each wave length of the given stimulus; (3) determine separately the areas of the three curves thus found; (4) reduce the three areal values thus obtained to percentage

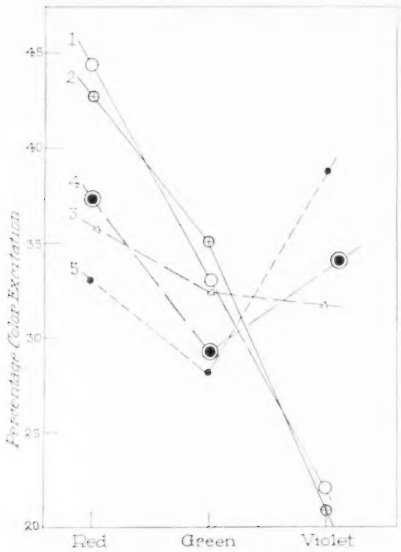


Fig. 10.—Percentage color excitation values: curve 1, normal blond; curve 2, normal brunette; curve 3, a case of polycythemia vera before treatment with phenylhydrazine; curve 4, the same case three weeks after treatment with phenylhydrazine was instituted, and curve 5, a case of Raynaud's disease during the stage of cyanosis.

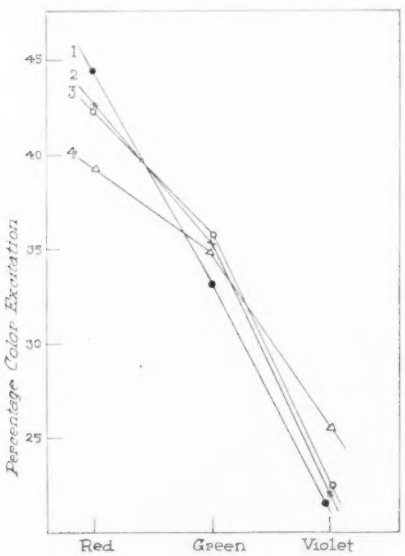


Fig. 11.—Percentage color excitation values: curve 1, normal brunette; curve 2, a case of Addison's disease; curve 3, a normal negro, and curve 4, a case of scleroderma.

form, so that their determined ratio remains unchanged but their sum becomes equal to 100. The color excitation values can then be expressed by means of two numbers, representing the red and violet excitation percentages, that for the green being obtainable by subtracting the sum of these two values from 100. Very complete details on these points are given in the report of the committee on colorimetry.[6]

Figure 8 contains the red, green and violet excitation curves for the spectrophotometric data given in curve 1 of figure 3, a case of a young normal blond. These excitation curves show the presence of spectral bands at 625, 570 and 530 to 540 millimicrons, respectively, as is evidenced also in figures 3 to 6. The conversion of the spectrophotometric curves into color excitation values (as outlined in the preceding paragraph) is much simplified and rendered more rapid by the use of a special slide rule prepared by Keuffel and Esser for this purpose.

We have followed the foregoing procedures in their applications to the curves of figures 3 to 6. In figures 9 to 11 are plotted the relationships existing between the fundamental color excitations (red, green and violet) and the percentage color excitations for normal blonds, normal brunettes, normal mulattoes and those affected with polycythemia vera, Addison's disease, Raynaud's disease and scleroderma. The data on the summated values for red, green and violet, as well as their percentages, are to be found in tables 1 and 2. In a general way the results of figures 9 to 11 show very conclusively that the relationship between percentage color excitation and wave length or color (red, green and violet) is approximately a linear one in normal persons in whom there are no abnormalities in quantity, quality or distribution of blood in the peripheral vessels and in whom the degree of pigmentation varies from slight to dense degrees. In cases of polycythemia vera, both before and after treatment with phenylhydrazine, and Raynaud's disease, in which there are abnormalities in the quantity, quality and distribution of the blood, we find that the analysis of the color of the skin into fundamental excitation color values shows marked reductions in red and green and marked increases in violet when compared with normal skin, which is either slightly or highly pigmented.

In addition to these data regarding the summated values and percentages of red, green and violet in the white light reflected from the skin, there is also a dominant wave length (hue) and a degree of purity or saturation. A dominant wave length and purity chart are reproduced in figure 12. Using the color triangle and taking the percentages of red and violet for the various curves of figures 3 to 6, we are able to find the dominant wave lengths (or hues), as well as the degrees of purity and relative luminosities, which are recorded in table 2. Figure 13 gives a résumé of the dominant wave lengths in various normal and pathologic conditions that we have investigated. It will be noted that

the dominant wave length is yellow (from 595 to 575 millimicrons) in cases of normals (blond, brunette and negro), Addison's disease and scleroderma. The dominant wave length in polycythemia vera is red (610 to 650 millimicrons) before treatment with phenylhydrazine but

TABLE 1.—*Color Excitation Values for Red, Green and Violet Obtained from the Spectrophotometric Data on the Skin of Normal Persons and in Certain Diseases*

Name	Figure	Curve	Clinical Classification	Total Red	Total Green	Total Violet	Remarks
J	9	1	Normal blond.....	2,000	2,186	1,340	Very fair complexion
	3	1					
P	10	2	Normal brunette.....	2,075	1,550	1,022	Average brunette
	6	2					
R	11	3	Normal negro.....	854	726	450	Average mulatto
M	3	2	Addison's disease.....	1,412	1,151	650	Advanced stage
	9	2					
L	11	4	Scleroderma.....	1,322	1,181	865	
	6	3					
T	10	5	Raynaud's disease.....	1,332	1,157	1,497	Cyanotic stage
H	9	3	Polycythemia vera....	1,570	1,425	1,388	Before treatment with phenylhydrazine
	4	All		1,970	1,790	1,566	After treatment with phenylhydrazine
W	9	4	Polycythemia vera....	1,264	1,127	1,200	Hand 30 cm. above heart level
				1,330	1,140	1,130	Hand 30 cm. below heart level

TABLE 2.—*Percentages of Color Excitation Values, Purity and Relative Luminosity, and Values of the Dominant Wave Length in the Skin of Normal Persons and in Certain Diseases*

Name	Figure	Curve	Clinical Classification	Red, per Cent	Green, per Cent	Violet, per Cent	Dominant Wave Length, Milli-microns	Purity, per Cent	Relative Luminosity, per Cent
J	9	1	Normal blond.....	42.4	35.7	21.9	587	43	34.8
	3	1							
P	10	2	Normal brunette.....	44.5	33.5	22.0	585	40	27.1
	6	2							
R	11	3	Normal negro.....	42.1	35.7	22.2	585	45	17.3
M	3	2	Addison's disease.....	43.9	35.7	20.4	580	50	19.4
	9	2							
L	11	4	Scleroderma.....	39.2	35.1	25.7	583	28	18.6
	6	3							
T	10	5	Raynaud's disease.....	33.4	28.0	38.6	527	25	17.4
H	9	3	Polycythemia vera.....	35.8	32.5	31.7	605	10	20.3
	4	All		37.1	29.4	33.5	497	20	25.3
W	9	4	Polycythemia vera.....	35.2	31.3	33.4	497	5	17.9
				36.9	31.6	31.5	640	10	18.0

it becomes greenish (497 to 510 millimicrons) after treatment with phenylhydrazine. This is on account of the high serum bilirubin and temporary jaundice created by reason of the large amount of hemoglobin broken down with the liberation of the pigments.

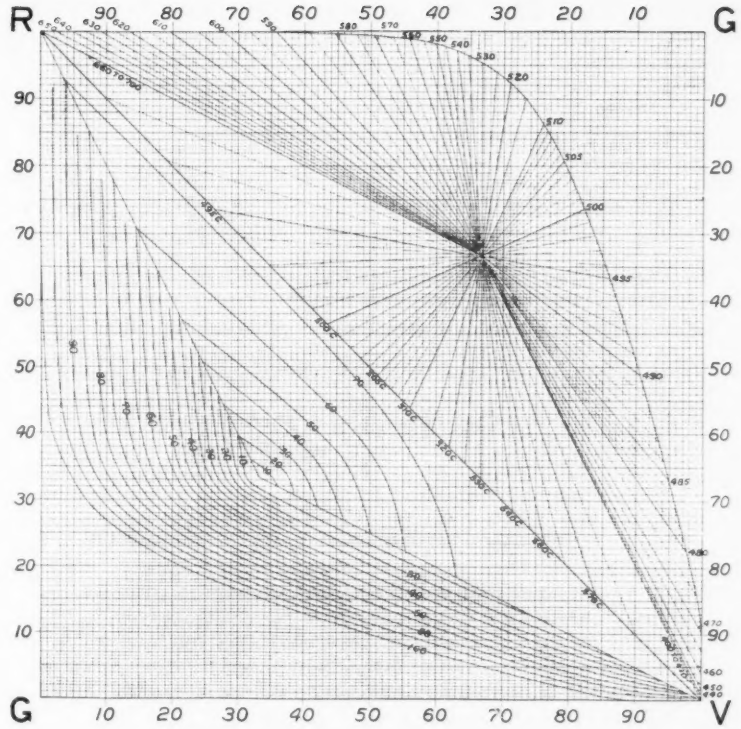


Fig. 12.—Dominant wave length and purity charts from which the hue and the degree of saturation may be obtained by the use of data from the percentage color excitation calculations.

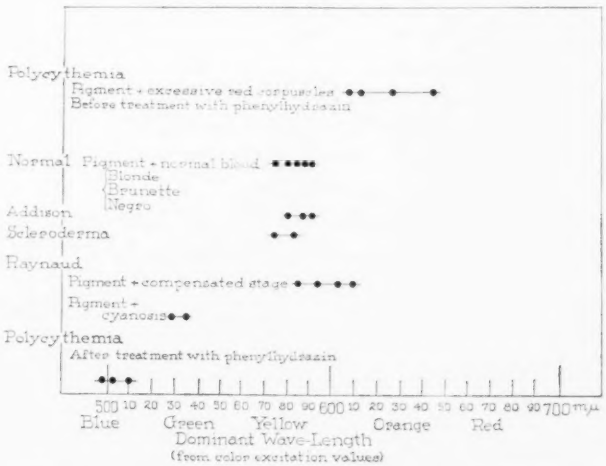


Fig. 13.—Relationships between the dominant wave lengths and various normal and pathologic conditions.

Tables 1 and 2 contain a full résumé of the spectrophotometric data and the analysis into excitation color curves, dominant wave length, percentage of purity and percentage of relative luminosity.

This method is being used or will be applied: (1) to determine quantitatively the melanin present in both normal and pathologic conditions; (2) to standardize or furnish a biologic rather than a physical unit for dosages of ultraviolet or superficial roentgen-ray treatments in terms of the changes produced in the color of the skin; (3) to coordinate the degree of pigmentation and changes in superficial distribution of blood with other physiologic effects or changes such as occur in rachitis, for example, and (4) to estimate the degree and character of the changes in the color of the skin before and after treatment in cases of Addison's disease, polycythemia, anemia, jaundice, hemachromatosis and other pathologic conditions in which there are departures from the normal in the color of the skin.

CONCLUSIONS

1. The spectrophotometric method of analysis of skin color furnishes the basis for a relatively simple but bloodless method of depicting certain characteristics of the blood at the peripheral portions of the body.

2. The spectrophotometric curves show the presence (or absence in certain cases) of (*a*) hematin, (*b*) reduced hemoglobin, (*c*) oxyhemoglobin, and possibly (*d*) methemoglobin in peripheral or superficial tissues and blood.

3. It is probable that the spectrophotometric data as obtained from the skin by reflection methods may be of value in determining certain physicochemical characteristics of the blood.

4. By spectrophotometric reflection curves and their subsequent analysis into fundamental red, green and violet excitation values, it is possible to differentiate between variations in skin color due to (*a*) pigment content and (*b*) the amount, distribution or quality of the peripheral blood supply.

5. Spectral analysis shows that there is close agreement in the values of the dominant wave length, purity and percentages of red, green and violet in normal blonds, brunettes and mulattoes and in such pathologic conditions as Addison's disease. The dominant wave length is practically 585 millimicrons (nearly sodium yellow) in all instances.

6. In cases of polycythemia vera, Raynaud's disease, during the stage of rubor, and allied conditions, there are marked departures from the normal condition in the values of the dominant wave lengths, purity and percentages of red, green and violet. In these diseases, in

which there are generally marked disturbances in the quantity, quality and distribution of blood, the dominant wave length is in the red (605 to 640 millimicrons in our observations).

7. Cyanosis is noticeable in various diseases. Spectrophotometric determinations and analyses in terms of monochromatic radiation show that the summated violet values are too high in comparison to similar summated values of the violet in normal subjects, and that there is a marked reduction in the summated values of the reds and greens in these diseases as compared with normal persons.

CORRECTION

In the article by Drs. Fahr and Swanson, "The Quantities of Serum Albumin, Globulin and Fibrinogen in the Blood Plasma in Acute and Chronic Nephropathies" (Arch. Int. Med. **38**:510 [Oct.] 1926) the authors desire to substitute "standard deviation" for "coefficient of deviation" in Table I and also in the sixteenth line of reading matter on page 512.

Book Reviews

NERVOUS AND MENTAL DISORDERS FROM BIRTH THROUGH ADOLESCENCE. By B. SACHS, M.D., and LOUIS HAUSMAN, M.D. Pp. 861. Price, $10. New York: Paul B. Hoeber, 1926.

Although based on a previous text (Nervous Diseases of Children, by B. Sachs, M.D.), this volume is enlarged and rewritten to constitute a new and comprehensive work of 861 pages with more than 100 illustrations. The format is pleasing and the bibliography recent.

The structure and function of the central nervous system are briefly considered and methods of examination outlined in the opening chapters. Meningitis and epidemic encephalitis are well described, especially the pathology and possible etiology of the latter, although one might wish in a work of this sort for a discussion of behavior disorders following encephalitis, in view of their rather frequent occurrence nowadays. Infantile cerebral palsies are thoroughly discussed, especially as to pathogenesis — aside from some recent work on the occurrence and early diagnosis and treatment of meningeal hemorrhage in the new-born infant.

Neurosyphilis in the young is so rare, the authors feel that it merits comparatively little space, juvenile paralysis being described in small type. On the other hand, amaurotic family idiocy, though even more rare, is covered at considerable length, in which, however, the authors show entirely pardonable preference for the Tay-Sachs disease. The chapter on the progressive muscular atrophies is especially good; it is a clear and complete discussion with an eight page bibliography. In connection with multiple sclerosis the latest work on pathology is reviewed at length, especially that of Hassin. The description of the striatal syndromes is brief. Brain tumors and lesions of the peripheral nerves are fully reviewed, and epilepsy, though briefly considered, is related to the more recent literature, including such therapeutic efforts as Peterman's ketogenic diet and Joseph Miller's advocacy of protein desensitization.

The account of hyperthyroidism, while detailed, fails to describe the condition as it occurs in children. The reviewer, with other readers, no doubt, has not seen hyperthyroidism in a child and would like to be informed wherein, if at all, the symptoms differ from those in an adult, if surgical intervention is indicated as in older patients, and like points. A similar criticism might be offered in connection with a few other topics, since in a text of this character one looks especially for a picture of the immature organism's reaction to deficiency, degeneration and disease.

The section dealing with the development and training of the normal child is notable for an attack on psychanalysis, summed up in the statements, "There is not a scintilla of scientific evidence in any part of this psychological doctrine. It is a speculation of the rankest sort." The authors state that to their knowledge many adolescents have been harmed by psychanalysis, and for this reason they are impelled to denounce its practice. Dementia praecox, manic depressive and defective mental development are all adequately treated, the first exceptionally well.

Altogether, this is an excellent treatise, which many general practitioners, pediatricians and others will doubtless find useful.

A BIPOLAR THEORY OF LIVING PROCESSES. By GEORGE W. CRILE. Edited by AMY F. ROLAND. Cloth. Price, $5. Pp. 405, with 62 illustrations. New York: The Macmillan Company, 1926.

The volume, according to the author, represents an attempt to present certain conclusions that are based on researches which have been in progress continuously from 1898 to the present time, and which were commenced to determine

the causes of fatigue, exhaustion and death. The researches followed four lines of study, the first three of which, circulation and respiration, blood chemistry and cytologic studies, gave no clue to the mechanism, the failure of which leads to fatigue, exhaustion and death. The fourth line of study, which the author terms biophysical studies, and of which the material of the book is composed, explains satisfactorily (to the author) the solution of the riddle, and leads to the formulation of the original and unique bipolar theory of life that represents a physical line of ascent from atom to man.

According to the theory, living matter is operated by electrical energy, and the author attempts to show that the materials of which animals are constructed are specifically adapted to electrical processes; that unit cells which drive the organism not only are adapted to fabricate, to store and to discharge electricity, but that protoplasm itself has these powers; that the organism as a whole is a bipolar electric mechanism bearing the pattern of the unit cells, and that the unit cells are constructed on the pattern of the atom; and, finally, that the normal and pathologic phenomena of man and animals can be interpreted in simple electrical terms.

In the proof of these ideas the author cites freely from the literature and more freely from his own experiments, some of which are not clear as to purpose, while others are based on a misinterpretation of fundamental physiologic facts. The experimental data, moreover, does not always bear on the points in question, and unwarranted conclusions are readily drawn. For example, in the attempt to substantiate the theory it is shown by experiment that the mammal is a bipolar mechanism, the positive pole of which is the brain while the negative pole, or "ground," is the liver. Thus, decerebration causes death simply by removing the positive pole of the battery, while liver ablation or disease that renders that organ nonfunctional removes the ground and produces death by making the circuit incomplete.

The theory embodies sound physiologic and chemical facts which are given electrical interpretations unreservedly and at times in neglect of other and better explanations of facts. The idea that all pathologic phenomena, including cancer, endocrine activity, reproduction and sex, etc., are the result of variations in electrical conductivity is unwarranted both from the evidence produced and from the known facts.

The material is presented in a pleasing manner; the book is well arranged and clearly expressed. It is interesting and original, but is of doubtful scientific value.

LES DIFFERENTES FORMES DE L'ARSENICISME. Par KARL PETREN. Cloth. Price, $10. Paris: Masson et Cie.

This volume is the French translation of the report of a commission of the Swedish government which investigated the subject of arsenicism exhaustively. In this edition the full case reports are omitted and only a few illustrative cases included. In its earlier stages this commission had the advantage of the services of Bang, and later of Ramberg and Wirgin, who elaborated microchemical methods by which infinitesimal amounts of arsenic could be accurately tested. Quantities as small as 0.0002 mg. in 10 cc. of blood can be recognized by this technic, which is based on the electrolytic reduction of arsenic at a mercury cathode.

In the first place, it was noted in an extensive analysis of foods that the fish from some regions of the Baltic as well as certain inland lakes contained appreciable amounts of arsenic, and that after ingestion of a single large meal of these fish the urine might contain as much as 1 mg. of arsenic. Whatever the physiologic effects of such a phenomenon, it is doubtful whether it is the cause of any real arsenical poisoning, although it may be the culminating factor in certain cases in which the body is already saturated almost to the point of toxemia.

After fish is eaten, the arsenic in the blood may rise to the level of 0.0004 mg. in 10 cc. of blood. Vigorous medication with a solution of potassium arsenite (Fowler's solution) raises the blood arsenic to 0.0012-0.0014 mg. in 10 cc., and a course of injections of arsphenamine may send these figures up to as high as 0.006 in 10 cc. However, such degrees of intoxication do not cause symptoms unless continued for a long period. Unfortunately, the true clinical cases of arsenicism were not submitted to blood tests, but in every case the exposure was at least six months, and more often it was a year. Reference is made to an epidemic of arsenicism that was caused by the prolonged ingestion in moderate amounts of beer that contained 4 mg. of arsenic per liter.

Probably most of the cases investigated by the commission resulted from arsenic in the wall-paper or paint on household goods. The arsenic in the wall-paper in these reports varied from 4 to 35 mg. in 200 sq. cm.

The clinical picture of this condition is quite constant. Headache, fatigue, falling hair and gastro-intestinal disturbances initiate the disease. As these become more severe, insomnia and vertigo come on. The mouth and gums become sore. Conjunctivitis of a mild type is frequent. Loss of appetite, nausea and, in many cases, even vomiting appear. The polyneuritis of arsenicism may be severe. Areas of anesthesia, paresthesia and motor paralyses, especially in the extremities, are common features in the severe cases.

DIE HYPERTONIEKRANKHEITEN. VON DR. ESKIL KYLIN, Direktor des Militärkrankenhauses in Eksjo, Sweden. Paper. Price, 8.40 marks. Pp. 168, with 22 illustrations. Berlin: Julius Springer, 1926.

The reviewer's task is not easy. This book contains a wealth of material on the newer aspects of hypertension, which if dug out from the unnecessary verbiage would form a fundamentally sound statement of facts and a stimulating array of theory. But it is extremely difficult to dig all this out.

The conception of a fundamental difference between essential hypertension and the hypertension of acute glomerulonephritis is well presented and discussed. Essential hypertension is the expression of an unknown result acting on the vegetative nervous system of certain persons of a peculiar constitutional make-up. There is in this disease no disturbance of the capillaries. The hypertension of glomerulonephritis is the result of injury to the capillary system. In neither instance need the kidney be primarily involved.

Most of the book is devoted to a discussion of the evidence leading to these conclusions. All interested in this vital problem should read the book.

BLOOD CHEMISTRY COLORIMETRIC METHODS. By W. J. STONE. Ed. 2. Pp 129. New York: Paul B. Hoeber.

The author limits the contents of this book to the determination of certain chemical constituents of the blood and urine which have some clinical significance, particularly in metabolic disturbances. Colorimetric methods for determining blood urea, nonprotein nitrogen, uric acid, creatinine, chlorides, sugar and cholesterol are described. A modification of Folin's method for estimating the total nitrogen of urine is added. The titratable acidity of the urine, a procedure of doubtful clinical importance, is also mentioned. The brief comments on the significance of the variations of the important chemical constituents of the blood, as well as the suggestions on the dietary management of nephritis and diabetes, are an added feature which many larger books on blood chemistry lack. The methods selected are reliable, are clearly stated, and require relatively small amounts of blood, and can be readily performed in a small laboratory. This volume should be a useful practical manual not only for practitioners, for whom it is intended, but also for workers in small clinical or hospital laboratories.

INDEX TO VOLUME 38

PAGE

Achlorhydria: See Stomach, acidity
Achylia Gastrica, pernicious anemia and combined cord degeneration and their relationship 292
Acids, organic, formation of, and retention of chlorides in lobar pneumonia..... 489
Ackman, F. D.: Combining power of proteins with rose bengal; application as quantitative test on spinal fluid..... 527
Aldrich, M.: Urea retention; simple method for its estimation by mercury combining power of blood..... 474
Alvarez, W. C.: Hypertension and constipation 158
Anaphylaxis, local, experimental production of gastric ulcer by..... 237
Andrews, E.: Water metabolism; sugar metabolism in dehydration..... 136
Anemia, pernicious 169
pernicious, achylia gastrica and combined cord degeneration and their relationship 292
splenic (Banti's disease)..... 171
Aneurysm, mycotic 226
mycotic, of aorta 367
Aorta, mycotic aneurysm of..... 367
stenosis of isthmus (coarctation) of; its diagnosis during life, 69; (correction). 409
Arachnidism: See Spider poisoning
Arrhythmia cordis, epigastric pulsation diagnosis of, through epigastriogram. 360
Aspiration, rationale of therapeutic puncture in pericardial effusions, experimental study 206
Atropine, effect of, on gastric function in man; quantitative study..... 303
Auricular fibrillation with regular ventricular rhythm and rate over 60..... 116

Baldridge, C. W.: Glandular fever; infectious Mononucleosis 413
Bazin, E. V.: Output of heart per beat in hyperthyroidism 566
Bellinger, M.: Chemical changes in blood during fasting in human subject..... 553
Benedict, F. G.: Insensible perspiration; its relation to human physiology and pathology 1
Beriberi, basal metabolism in..... 770
Berk, A.: Sodoku in treatment of general paralysis; preliminary report..... 391
Bile, regulation of flow of, and pancreatic juice into duodenum..... 647
Biliary Tract, chronic disease of; diagnostic criteria 708
Blister, capillary permeability and inflammatory index of skin in normal person as determined by..... 663
Blood, changes in chemical and physical characteristics of, following administration of parathyroid hormone; with special reference to clotting of blood. 502
chemical changes in, during fasting in human subject 553
pressure, high, and constipation..... 158
pressure, high, basal metabolic rate in cases of chronic cardiac disease and.. 385
pressure, systolic and diastolic, relative importance of, in maintaining coronary circulation 109
quantities of serum albumin, globulin and fibrinogen in blood plasma in acute and chronic nephropathies 510
tests, aid in diagnosis of typhoid fever; new laboratory method..... 544
urea retention; simple method for its estimation by mercury combining power of blood 474
Bloomfield, A. L.: Clinical physiology of stomach; simultaneous quantitative observations on gastric secretory volume, acidity and motility..... 145

Bloomfield, A. L.—Continued PAGE
Effect of atropine on gastric function in man, quantitative study..... 303
Method for continuous quantitative estimation of gastric secretion and discharge in man, (correction)..... 141
Bogen, E.: Arachnidism; spider poisoning. 623
Boles, R. S.: Nontraumatic left diaphragmatic hernia; clinical and roentgenologic studies in 15 cases..... 633
Bone, defective development in, renal dwarfism; report of case..... 612
long, growth of, in childhood; with special reference to certain bony striations of metaphysis and to rôle of vitamins. 785
Book Reviews:
A Bipolar Theory of Living Processes; G. W. Crile..... 832
Archives of Andrew Todd McClintock Memorial Foundation for the Study of Diseases of Alimentary Canal; Pleomorphism in Bacterial Protoplasm; Study in Psittacosis; A. T. McClintock 143
Art of Medical Treatment; F. W. Palfrey 143
Blood Chemistry Colorimetric Methods; W. J. Stone..... 834
Classification of Strains Belonging to Typhoid-Paratyphoid Group of Bacteria Together with Demonstration of Differences in Avidity; A. Hecht-Johansen 412
Development of Our Knowledge of Tuberculosis; L. F. Flick..... 278
Die Hypertoniekrankheiten; E. Kylin.. 834
Diseases of the Heart; H. Vaquez..... 410
Facts on the Heart; R. C. Cabot..... 551
Fibrilacion y Flutter Auricular; M. Vela Gonzalez 552
Food for Diabetic; M. P. Hussleson.... 412
Gastric Function in Health and Disease; J. A. Ryle..... 276
Immunochemical Studies; C. H. Browning 276
Investigations into Morphology of Ray Fungi; J. Orskov..... 412
La Arteritis Pulmonar, Cardiacos Negros; F. C. Arrillaga..... 278
Les Differentes Formes de l'Arsenicisme; K. Petren..... 833
Les Maladies Des Glandes Endocrines; K. H. Krabbe..... 684
Le Terrain Heredo-Syphilitique; V. Hutinel 683
Manual of Clinical Laboratory Methods; C. L. Cummer..... 277
Medical Diagnosis; J. M. Anders and L. Napoleon..... 411
Nephritis; H. Elwyn..... 277
Nervous and Mental Disorders from Birth Through Adolescence; B. Sachs and L. Hausman..... 832
Physical Diagnosis of Diseases of the Chest; Pratt & Bushnell..... 411
Physiotherapy; H. E. Stewart..... 142
Psychoanalysis and Beyond Psychoanalysis; L. L. Landis..... 277
Rheumatic Heart Disease; C. F. Coombs. 551
Scoliosis; S. Kleinberg..... 276
Studies of Gonococcus Types and Gonococcus Immune Serums; E. Vollmond 412
Studies on Papillae Vallatae of Man; A. Jurisch 412
Synopsis of Medicine; H. L. Tidy..... 142
The International Medical Annual; A Year Book of Treatment and Practitioner's Index. Forty-Fourth Year, 1926 684
The Principles and Practice of Endocrine Medicine; W. N. Berkeley..... 682

PAGE

Brown, G. E.: Spectrophotometric analysis of color of skin; and observations by this method in normal and pathologic subjects 816
Treatment of polycythemia vera (erythremia) with phenylhydrazine..... 321

Cantarow, A.: Changes in chemical and physical characteristics of blood following administration of parathyroid hormone; with special reference to clotting of blood..... 502
Modification of urea concentration test. 581
Capillary permeability and inflammatory index of skin in normal person as determined by blister..... 663
permeability, relation of menstruation to autonomic tonus of skin vessels and. 730
Carcinoma of cortex of suprarenal gland with virilism; case with necropsy.... 469
primary, of thymus..... 807
Caven, W. R.: Changes in chemical and physical characteristics of blood following administration of parathyroid hormone; with special reference to clotting of blood..... 502
Cerebrospinal Fluid, tests, combining power of proteins with rose bengal; application as quantitative test on spinal fluid 527
Chloride, retention, formation of organic acids and, in lobar pneumonia..... 489
retention; unitary nature of impairment of renal function..... 268
Clay, C. L.: Sodoku in treatment of general paralysis, preliminary report..... 391
Cocaine, poisoning, acute; its treatment in monkey (Macacus rhesus)..... 405
Collins, K. H.: Acute cocaine poisoning and its treatment in monkey (Macacus rhesus) 405
Conner, H. M.: Diseases of liver; comparative study of tests for hepatic function in certain diseases of hematopoietic system 167
Constipation and hypertension..... 158
Contractions, persistent premature, clinical study 186
Copher, G. H.: Regulation of flow of bile and pancreatic juice into duodenum.. 647
Coronary circulation, relative importance of systolic and diastolic blood pressure in maintaining 109
thrombosis, with congenital absence of left coronary artery 222

Diabetes Mellitus, benign glycosuria in diabetic families 279
hyperthyroidism, myxedema and..... 736
insulin by mouth 779
rôle of insulin in protein metabolism.... 96
Dodge, H. F.: Analysis of heart sounds... 685
Duodenum, regulation of flow of bile and pancreatic juice into..... 647
ulcer: See Peptic Ulcer
Dwarfism, renal; report of case..... 612
Dynomometer, cardiac capacity determined by standardized effort; preliminary report 761

Edema; correlation of elastometer findings, disappearance time for intradermally injected salt solution, urinalysis and nitrogen retention of blood in edema. 57
pharmacology and therapeutics of novasurol 374
Elastometer findings, correlation of, disappearance time for intradermally injected salt solution, urinalysis and nitrogen retention of blood in edema.. 57
Elwyn, H.: Pathogenesis of lipoid nephrosis 346
Epigastric pulsation; diagnosis of arrhythmia cordis through epigastriogram.... 360
Erysipelas, roentgen-ray therapy in..... 573
Erythremia: See Polycythemia
Ets, H. N.: Rationale of therapeutic puncture in pericardial effusions..... 206

Fahr, G.: Quantities of serum albumin, globulin and fibrinogen in blood plasma in acute and chronic nephropathies... 510

PAGE

Fasting, chemical changes in blood during, in human subject..... 553
Feinblatt, H. M.: Carcinoma of cortex of suprarenal gland with virilism; case with necropsy..... 469
Fishberg, A. M.: Unitary nature of impairment of renal function..... 259
Fleisher, M. S.: Relation of monilia to infections of upper air passages..... 217
Fukui, N.: Epigastric pulsation; diagnosis of arrhythmia cordis through epigastriogram 360

Galambos, A.: Direct examination of gastric juice; new functional test..... 654
Gallbladder, chronic biliary tract disease; diagnostic criteria..... 708
Giffin, H. Z.: Treatment of polycythemia vera (erythremia) with phenylhydrazine 321
Glandular fever; infectious mononucleosis. 413
Glycosuria, benign, occurrence of, in diabetic families 279
Gold, H.: Persistent premature contractions; clinical study..... 186
Gordon, B.: Changes in chemical and physical characteristics of blood following administration of parathyroid hormone; with special reference to clotting of blood 502
Graber, V. C.: Coronary thrombosis with congenital absence of left coronary artery 222
Relative importance of systolic and diastolic blood pressure in maintaining coronary circulation 109
Greene, C. H.: Diseases of liver; comparative study of tests for hepatic function in certain diseases of hematopoietic system 167
Grinker, R. R.: Pernicious anemia, achylia gastrica and combined cord degeneration and their relationship..... 292

Hansmann, G. H.: Glandular fever; infectious mononucleosis 413
Mycotic aneurysm of aorta..... 367
Harris, H. A.: Growth of long bones in childhood; with special reference to certain bony striations of metaphysis and to rôle of vitamins..... 785
Heart, auricular fibrillation with regular ventricular rhythm and rate over 60.. 116
cardiac capacity determined by standardized effort; preliminary report..... 761
diseases, chronic, basal metabolic rate in, and in hypertension..... 385
output of, per beat in hyperthyroidism.. 566
sounds, analysis of..... 685
Hematopoietic System, diseases of liver; comparative study of tests for hepatic function in certain diseases of hematopoietic system 167
Hench, P. S.: Urea retention; simple method for its estimation by mercury combining power of blood..... 474
Henderson, W. S.: Chronic biliary tract disease; diagnostic criteria..... 708
Heredity, occurrence of benign glycosuria in diabetic families 279
Hernia, diaphragmatic, nontraumatic left; clinical and roentgenologic studies in 15 cases 633
Hines, L. E.: Peristalsis in loop of small intestine; direct study..... 536
Holst, J. E.: Occurrence of benign glycosuria in diabetic families..... 279
Holten, C.: Formation of organic acids and retention of chlorides in lobar pneumonia 489
Hypertension: See Blood pressure, high
Hyperthyroidism, external factors causing variable results in Kottmann reaction. 129
myxedema, diabetes and..... 736
output of heart per beat in..... 566
Hypnotics in acute cocaine poisoning..... 405

Insulin, rôle of, in protein metabolism.... 96
use of, by mouth..... 779

PAGE

Intestines, motility, peristalsis in loop of small intestine; direct study..... 536
Ivy, A. C.: Gastric ulcer; experimental production of gastric ulcer by local anaphylaxis 237

Janney, N. W.: Rôle of insulin in protein metabolism 96
Japanese, basal metabolism of..... 590
Jaundice, hemolytic 168
Jones, H. W.: Modification of urea concentration test 581

Kameda, T.: Basal metabolism of Japanese 590
Kasanin, J.: External factors causing variable results in Kottmann reaction. 129
Kawahara, S.: Rate of urea excretion as test of renal function by means of modification of McLean's index..... 36
Keefer, C. S.: Clinical physiology of stomach; simultaneous quantitative observations on gastric secretory volume, acidity and motility..... 145
Effect of atropine on gastric function in man, quantitative study..... 303
Kidney diseases, lipoid nephrosis..... 449
diseases, pathogenesis of lipoid nephrosis 346
diseases, quantities of serum albumin, globulin and fibrinogen in blood plasma in acute and chronic nephropathies... 510
function, unitary nature of impairment of 259
function test, modification of urea concentration test 581
function test, rate of urea excretion as test of renal function by means of modification of McLean's index..... 36
function test, urea retention; simple method for its estimation by mercury combining power of blood..... 474
insufficiency, renal dwarfism; report of case 612
pharmacology and therapeutics of novasurol 374
King, J. T., Jr.: Stenosis of isthmus (coarctation) of aorta and its diagnosis during life, 69; (correction)..... 409
Kitzmiller, K. V.: Aid in diagnosis of typhoid fever; new laboratory method. 544
Knapp, E.: External factors causing variable results in Kottmann reaction. 129
Kodama, S.: Regulation of flow of bile and pancreatic juice into duodenum.. 647
Kotkis, A. J.: Relation of monilia to infections of upper air passages..... 217
Kottmann Reaction: See Thyroid function test
Kunde, M. M.: Edema; correlation of elastometer findings, disappearance time for intradermally injected salt solution, urinalysis and nitrogen retention of blood in edema..... 57

Lathrop, F. W.: Renal dwarfism..... 612
Leas, R. D.: Mycotic aneurysms..... 226
Lemann, I. I.: Primary carcinoma of thymus; report of case..... 807
Lennox, W. G.: Chemical changes in blood during fasting in human subject..... 553
Leukemia 176
Levy, R. L.: Auricular fibrillation with regular ventricular rhythm and rate over 60 116
Lipoid nephrosis 449
nephrosis, pathogenesis of..... 346
Liver diseases, comparative study of tests for hepatic function in certain diseases of hematopoietic system..... 167

McCalla, R. L.: Hypertension and constipation; statistical inquiry..... 158
McLean's Index: See Kidney, function test
Mateer, J. G.: Chronic biliary tract disease; diagnostic criteria..... 708
Mead, H. C. A.: Peristalsis in loop of small intestine; direct study..... 536
Menstruation, relation of, to permeability of skin capillaries and autonomic tonus of skin vessels..... 730

PAGE

Mental Disease, external factors causing variable results in Kottmann reaction. 129
Mercury, urea retention; simple method for its estimation by mercury combining power of blood..... 474
Metabolism: See also Protein metabolism; Sugar metabolism; Water metabolism
basal, in beriberi..... 770
basal metabolic rate in cases of chronic cardiac disease and in cases of hypertension 385
basal, of Japanese 590
chemical changes in blood during fasting in human subject..... 553
insensible perspiration; its relation to human physiology and pathology..... 1
Metaphysis, growth of long bones in childhood; with special reference to certain bony striations of metaphysis and to rôle of vitamins..... 785
Miller, G. H.: Relative importance of systolic and diastolic blood pressure in maintaining coronary circulation..... 109
Miller, H. R.: Use of insulin by mouth... 779
Milles, G.: Relation of menstruation to permeability of skin capillaries and autonomic tonus of skin vessels..... 730
Mills, C. A.: Aid in diagnosis of typhoid fever; new laboratory method..... 544
Monilia, relation of, to infections of upper air passages 217
Mononucleosis: See under Glandular Fever
Murphy, F. D.: Lipoid nephrosis..... 449
Mycotic aneurysms, 2 cases..... 226
aneurysm of aorta..... 367
Myxedema, hyperthyroidism, diabetes and. 736

Nitrogen retention of blood in edema, correlation of elastometer findings, disappearance time for intradermally injected salt solution, urinalysis and.. 57
Novasurol, pharmacology and therapeutics of 374

O'Connor, M.: Chemical changes in blood during fasting in human subject..... 553
Okada, S.: Basal metabolism in beriberi.. 770
Basal metabolism of Japanese..... 590
Otto, H. L.: Persistent premature contractions; clinical study..... 186

Pain, mechanism of, in gastric and duodenal ulcers; achlohydria 603
mechanism of, in gastric and duodenal ulcer; production of pain by means of chemical irritants..... 694
Palmer, W. L.: Mechanism of pain in gastric and duodenal ulcers; achlorhydria 603
Mechanism of pain in gastric and duodenal ulcer; production of pain by means of chemical irritants..... 694
Pancoast, H. K.: Nontraumatic left diaphragmatic hernia; clinical and roentgenologic studies in 15 cases..... 633
Pancreatic juice, regulation of flow of bile and, into duodenum..... 647
Paralysis, general, sodoku in treatment of.. 391
Parathyroid hormone, changes in chemical and physical characteristics of blood following administration of; with special reference to clotting of blood..... 502
Peptic Ulcer, experimental production of gastric ulcer by local anaphylaxis.... 237
gastric and duodenal ulcer; frequency, number, size, shape, location, color, sex and age in 7,700 necropsy records at Bellevue Hospital, New York..... 41
mechanism of pain in gastric and duodenal ulcers; achlorhydria..... 603
mechanism of pain in gastric and duodenal ulcer; production of pain by means of chemical irritants..... 694
Pericardial effusions, rationale of therapeutic puncture in, experimental study 206
Peristalsis: See Intestines, motility
Perspiration, insensible; its relation to human physiology and pathology..... 1
Petersen, W. F.: Capillary permeability and inflammatory index of skin in normal person as determined by blister..... 663

Petersen, W. F.—Continued PAGE
Relation of menstruation to permeability of skin capillaries and autonomic tonus of skin vessels..... 730
Phenylhydrazine, treatment of polycythemia vera (ervthremia) with..... 321
Platou, E. S.: Roentgen-ray therapy in erysipelas 573
Pneumonia, formation of organic acids and retention of chlorides in..... 489
Polycythemia vera (erythremia)..... 175
vera (erythremia), treatment of, with phenylhydrazine 321
Protein, combining power of, with rose bengal; application as quantitative test on spinal fluid..... 527
metabolism, rôle of insulin in..... 96

Rabinowitch, I. M.: Output of heart per beat in hyperthyroidism..... 566
Respiratory Tract, infections, relation of monilia to 217
Rigler, L.: Roentgen-ray therapy in erysipelas 573
Roentgen-ray therapy in erysipelas..... 573
Rohner, F. J.: Glandular fever; infectious mononucleosis 413
Root, H. F.: Insensible perspiration; its relation to human physiology and pathology 1
Rose Bengal Test: See under Proteins
Rosenthal, S. M.: Combining power of proteins with rose bengal; application as quantitative test on spinal fluid..... 527

Sakurai, E.: Basal metabolism in beriberi. 770
Basal metabolism of Japanese..... 590
Salt solution, edema; correlation of elastometer findings, disappearance time for intradermally injected salt solution, urinalysis and nitrogen retention of blood in edema..... 57
Serby, A. M.: Pharmacology and therapeutics of novasurol..... 374
Shapiro, I.: Rôle of insulin in protein metabolism 96
Shapiro, L. L.: Gastric and duodenal ulcer; frequency, number, size, shape, location, color, sex and age in 7,700 necropsy records at Bellevue Hospital, New York 41
Shapiro, P. F.: Gastric ulcer; experimental production of gastric ulcer by local anaphylaxis 237
Shapiro, S.: Basal metabolic rate in cases of chronic cardiac disease and in cases of hypertension 385
Sheard, C.: Spectrophotometric analysis of color of skin; and observations by this method in normal and pathologic subjects 816
Skin, capillary permeability and inflammatory index of, in normal person as determined by blister..... 663
capillaries, relation of menstruation to permeability of, and autonomic tonus of skin vessels..... 730
spectrophotometric analysis of color of; and observations by this method in normal and pathologic subjects..... 816
Smith, F. M.: Coronary thrombosis with congenital absence of left coronary artery 222
Mycotic aneurysm of aorta..... 367
Relative importance of systolic and diastolic blood pressure in maintaining coronary circulation 109
Smith, J.: Primary carcinoma of thymus; report of case..... 807
Sodoku in treatment of general paralysis.. 391
Solomon, H. C.: Sodoku in treatment of general paralysis, preliminary report.. 391
Spectrophotometric analysis of color of skin; and observations by this method in normal and pathologic subjects..... 816
Spider poisoning; arachnidism..... 623
Spinal Cord, degeneration, relationship of pernicious anemia, achylia gastrica and 292

PAGE
Splenomegaly of Gaucher type..... 173
Stomach, acidity, mechanism of pain in gastric and duodenal ulcers; achlorhydria 603
direct examination of gastric juice; new functional test 654
effect of atropine on gastric function in man; quantitative study..... 303
gastric secretion and discharge, method for continuous quantitative estimation of, (correction) 141
simultaneous quantitative observations on gastric secretory volume, acidity and motility 145
ulcer: See Peptic Ulcer
Sturtevant, M.: Gastric and duodenal ulcer; frequency, number, size, shape, location, color, sex and age in 7,700 necropsy records at Bellevue Hospital, New York 41
Sugar metabolism in dehydration..... 136
Suprarenals, carcinoma of cortex of, with virilism; case with necropsy..... 469
Swanson, W. W.: Quantities of serum albumin, globulin and fibrinogen in blood plasma in acute and chronic nephropathies 510

Tatum, A. L.: Acute cocaine poisoning and its treatment in monkey (Macacus rhesus) 405
Thatcher, H. S.: Mycotic aneurysms..... 226
Theiler, M.: Sodoku in treatment of general paralysis, preliminary report.... 391
Thrombosis, coronary, with congenital absence of left coronary artery..... 222
Thymus, primary carcinoma of; report of case 807
Thyroid, function test, external factors causing variable results in Kottmann reaction 129
Typhoid, diagnosis of; new laboratory method 544

Urea concentration test, modification of... 581
excretion, rate of, as test of renal function by means of modification of McLean's index 36
retention; simple method for its estimation by mercury combining power of blood 474
Uremia, unitary nature of impairment of renal function..... 259
Urine, analysis, edema; correlation of elastometer findings, disappearance time for intradermally injected salt solution, urinalysis and nitrogen retention of blood in edema..... 57
in impaired renal function..... 266

Virilism, carcinoma of cortex of suprarenal gland with; case with necropsy..... 469
Vitamins, growth of long bones in childhood; with special reference to certain bony striations of metaphysis and to rôle of vitamins..... 785

Wachowiak, M.: Relation of monilia to infections of upper air passages..... 217
Warfield, L. M.: Lipoid nephrosis..... 449
Water metabolism; sugar metabolism in dehydration 136
Wilder, R. M.: Hyperthyroidism, myxedema and diabetes 736
Williams, H. B.: Analysis of heart sounds 685
Williamson, C. S.: Rationale of therapeutic puncture in pericardial effusions; experimental study 206
Willis, D. A.: Capillary permeability and inflammatory index of skin in normal person as determined by blister..... 663
Wolffe, J. B.: Cardiac capacity determined by standardized effort; preliminary report 761

Zimmermann, A.: Hypertension and constipation; statistical inquiry..... 158

THE ARCHIVES OF INTERNAL MEDICINE is published by the American Medical Association for the advancement of scientific medicine in the United States and as a medium of publication for research and observation in the domain of internal medicine.

Manuscripts for publication, books for review, and correspondence relating to the editorial management should be sent to Dr. Joseph L. Miller, Editor-in-Chief, 122 South Michigan Boulevard, Chicago, or to any other member of the Editorial Board. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF INTERNAL MEDICINE, American Medical Association, 535 North Dearborn Street, Chicago.

Articles are accepted for publication on condition that they are contributed solely to the ARCHIVES OF INTERNAL MEDICINE. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones of illustrations will be supplied by the Association when the original illustrations warrant.

Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index, published by the American Medical Association. This requires, in order given: name of author, title of article, name of periodical, with volume, page, month—day of month if weekly—and year. A complete list of abbreviations for standard periodicals, together with a full discussion of the style of the A. M. A. publications, appears in The Art and Practice of Medical Writing, a comprehensive book on the preparation of medical manuscripts, published by the American Medical Association. Price, $1.50.

Matter appearing in the ARCHIVES OF INTERNAL MEDICINE is covered by copyright but, as a rule, no objection will be made to its reproduction in reputable medical journals, if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the ARCHIVES OF INTERNAL MEDICINE, or in any of the other publications issued by the Association, will not be permitted.

Authors will receive one hundred reprints free; additional reprints may be obtained at cost.

The ARCHIVES OF INTERNAL MEDICINE is published monthly. Annual subscription price (two volumes): Domestic, $5.00; Canadian, $5.40; foreign, $5.75, including postage. Single copies, 75 cents, postpaid.

Checks, etc., should be made payable to the AMERICAN MEDICAL ASSOCIATION.

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (two volumes): Domestic, $5.00; Canadian, $6.50; foreign, $7.50. Single copies, 20 cents.

AMERICAN JOURNAL OF DISEASES OF CHILDREN—Monthly. Presents pediatrics as a medical science and as a social problem. It includes carefully prepared collective abstracts based on recent pediatric literature, abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $4.00; Canadian, $4.30; foreign, $4.50. Single copies, 50 cents.

ARCHIVES OF NEUROLOGY AND PSYCHIATRY—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions and full abstracts of the literature on these two subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

ARCHIVES OF SURGERY—Monthly. Devoted largely to the investigative and clinical phases of surgery, with monthly reviews on orthopedic and urologic surgery. Well illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

ARCHIVES OF OTOLARYNGOLOGY—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, the transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

ARCHIVES OF PATHOLOGY AND LABORATORY MEDICINE—Monthly. A periodical devoted to the publication of original contributions in the field of pathology, with abstracts from foreign and domestic literature, book reviews, the transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

QUARTERLY CUMULATIVE INDEX TO CURRENT MEDICAL LITERATURE—Quarterly. A complete subject and author index to the worth-while current medical literature of the world. Issued four times a year. Second and fourth volumes bound for permanent reference. Subscription price, calendar year: Domestic, $8.00; Canadian, $8.50; foreign, $8.75.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn St. CHICAGO

CONTENTS

PAGE

Analysis of Heart Sounds. H. B. Williams, M.D., and H. F. Dodge, S.B., A.M., New York 685

The Mechanism of Pain in Gastric and in Duodenal Ulcer: II. The Production of Pain by Means of Chemical Irritants. Walter Lincoln Palmer, M.D., Chicago 694

Chronic Biliary Tract Disease: The Diagnostic Criteria. John G. Mateer, M.D., and W. Stuart Henderson, M.D., Detroit 708

The Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels. William F. Petersen, M.D., and George Milles, S.B., Chicago 730

Hyperthyroidism, Myxedema and Diabetes. Russell M. Wilder, M.D., Rochester, Minn. 736

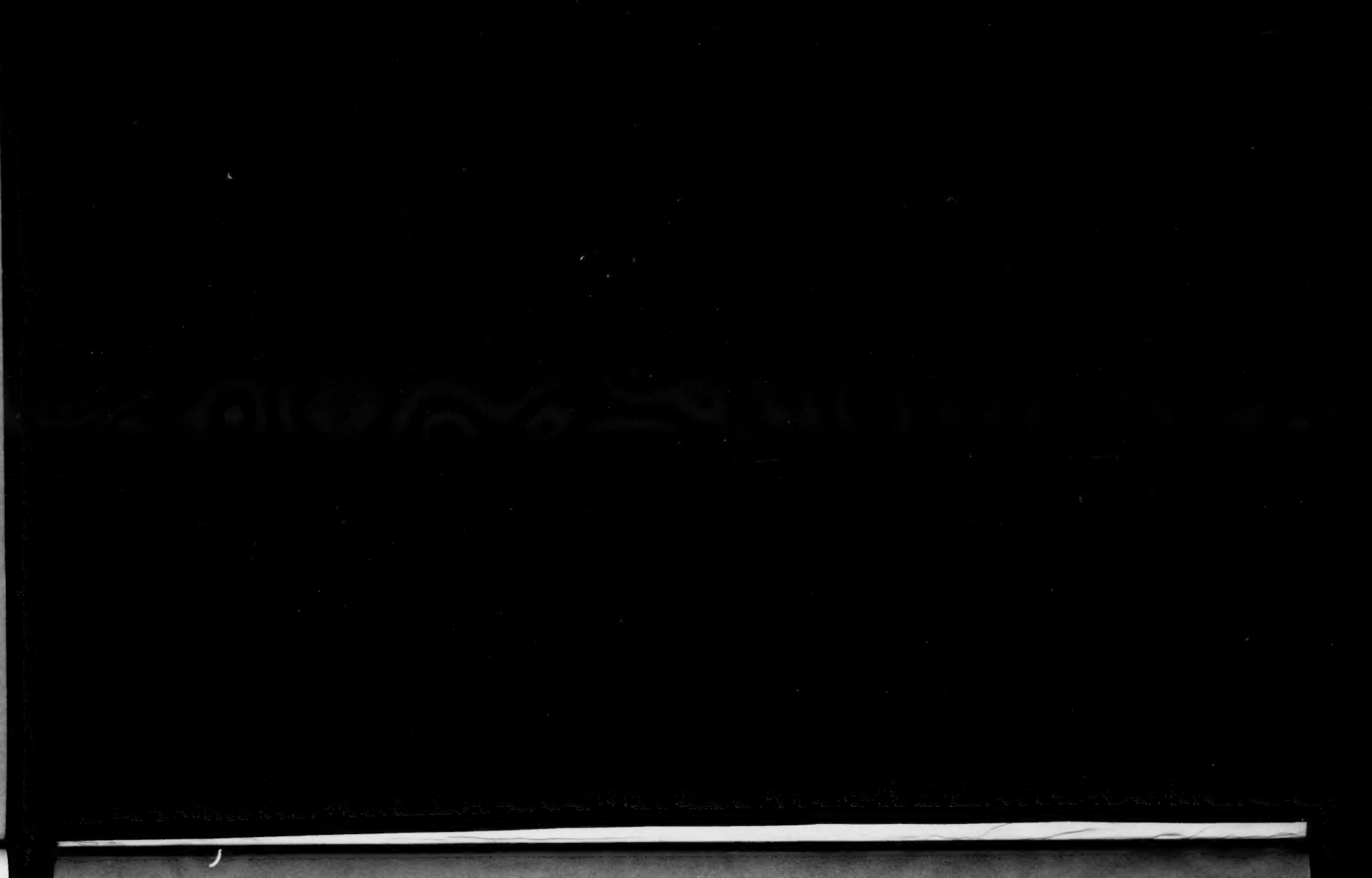
Cardiac Capacity Determined by Standardized Effort: Preliminary Report. Joseph B. Wolffe, M.D., Philadelphia 761

The Basal Metabolism in Beriberi. Seizaburo Okada and Eiichi Sakurai, Tokyo, Japan 770

The Use of Insulin by Mouth. H. R. Miller, M.D., New York 779

The Growth of the Long Bones in Childhood, with Special Reference to Certain Bony Striations of the Metaphysis and to the Rôle of the Vitamins. H. A. Harris, M.B., St. Louis 785

Primary Carcinoma of the Thymus: Report of a Case. I. I. Lemann, M.D., and John Smith, M.D., New Orleans 807

The Spectrophotometric Analysis of the Color of the Skin, and the Observations by this Method in Normal and in Pathologic Subjects. Charles Sheard, Ph.D., and George E. Brown, M.D., Rochester, Minn. 816

Book Reviews 832